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HPV-Related Cancers in Bosnia and Herzegovina: A Comprehensive Review

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Abstract
This review assesses the burden of human papillomavirus (HPV)-related cancers in Bosnia and Herzegovina (BH), aiming to inform strategies for prevention and early detection. Despite the availability of highly effective HPV vaccines and screening programs, HPV-related cancers remain a significant public health burden worldwide. We conducted a comprehensive search of PubMed and GLOBOCAN to identify all available data on HPV prevalence/genotype and HPV-related malignancies in BH, including information on HPV vaccination and cervical cancer screening. A comprehensive literature search revealed limited data on HPV prevalence and HPV-related cancers, as well as the absence of a national HPV vaccination or cervical cancer screening program in BH. In the largest study with available data from BH, HPV prevalence was 43% among women undergoing routine gynecologic exams. HPV-16 was identified as the most common cause of cervical cancer. The HPV prevalence was 50% in head and neck cancer, with HPV-18 being the most prevalent subtype. HPV was detected in 80% of patients with colorectal cancer, and HPV-16 was the most common subtype. **Conclusions.** HPV-related cancers, particularly cervical cancer, represent a significant public health problem in BH. Implementation of a national HPV vaccination program, along with organized cervical cancer screening is essential to reduce HPV-related morbidity and mortality. Addressing systemic challenges, such as establishing a comprehensive cancer registry, is essential for effective HPV prevention and control. Raising public awareness about HPV infection, its consequences, and the importance of prevention is essential for vaccine acceptance and promoting healthy behaviors. By investing in HPV prevention, BH can significantly improve the health and well-being of its population, particularly women.

Key Words: Human Papillomavirus ▪ Bosnia and Herzegovina ▪ Cancers ▪ Vaccination ▪ Screening.

Introduction

Overview of Human Papillomavirus (HPV) and Its Association with Various Cancers

The HPV virus is a small deoxyribonucleotide acid (DNA) virus that is the most common cause of sexually transmitted diseases worldwide. HPV is primarily transmitted through sexual contact, including vaginal, anal, and oral sex. While most HPV infections are asymptomatic and resolve spontaneously, persistent infections with certain high-risk HPV subtypes can lead to precancerous changes and ultimately cancer. There are over 200 identified HPV subtypes, but only 12 are considered high-risk and linked to cancer development (1). Cervical cancer is the most recognized HPV-related malignancy. HPV-16 and 18 are primarily responsible for its development. However, HPV's oncogenic potential extends beyond the cervix. It is a significant causative factor in other anogenital cancers, including vaginal, vulvar, anal, and penile cancers. It is a primary cause of vaginal and vulvar cancers, contributing to approximately 75% and 69% of cases, respectively (2). Globally, there has been a substantial increase in HPV-related oropharyngeal cancers, linked to rising rates of sexually transmitted HPV infection. HPV-related oropharyngeal cancers generally have a more favorable prognosis compared

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to those not associated with HPV (3). While less prevalent, HPV is also linked to cancers of the oral cavity and larynx, although the prevalence of HPV in these cancers is lower compared to oropharyngeal cancer (4).

Prevention and early detection are crucial in reducing the burden of HPV-related diseases. HPV infection can be effectively prevented through vaccination with one of three available HPV vaccines: bivalent, quadrivalent, and 9-valent (5, 6). These vaccines target both low-risk and high-risk HPV subtypes, with all three protecting against high-risk HPV subtypes 16 and 18, which are responsible for most HPV-related cancers. Early detection of asymptomatic precancerous lesions caused by HPV infection through screening tests is crucial for preventing invasive cancer.

Importance of Studying HPV-related Cancers in BH

Cancer represents a major public health concern globally, including in BH. According to GLOBOCAN data, an estimated 14,265 new cancer cases are diagnosed annually in BH, resulting in approximately 8590 cancer-related deaths each year (7). HPV is responsible for approximately 790,000 cancers worldwide each year, accounting for about 5% of all cancers (8). Despite being a globally recognized preventable disease, BH faces substantial gaps in HPV prevention and control. The absence of a unified national cervical cancer screening program and HPV vaccination rates contributes to a high risk of HPV-related cancers among the population. Cervical cancer is the most common cancer among these cases and a leading cause of cancer-related deaths in women in developing countries (Figure 1). The situation in BH is further complicated by high rates of high-risk HPV infections among women of reproductive age and the absence of a national cervical cancer screening or vaccination program (9). The prevalence of high-risk HPV subtypes 16 and 18 among women of reproductive age further underscores the urgent need for effective prevention and control measures.

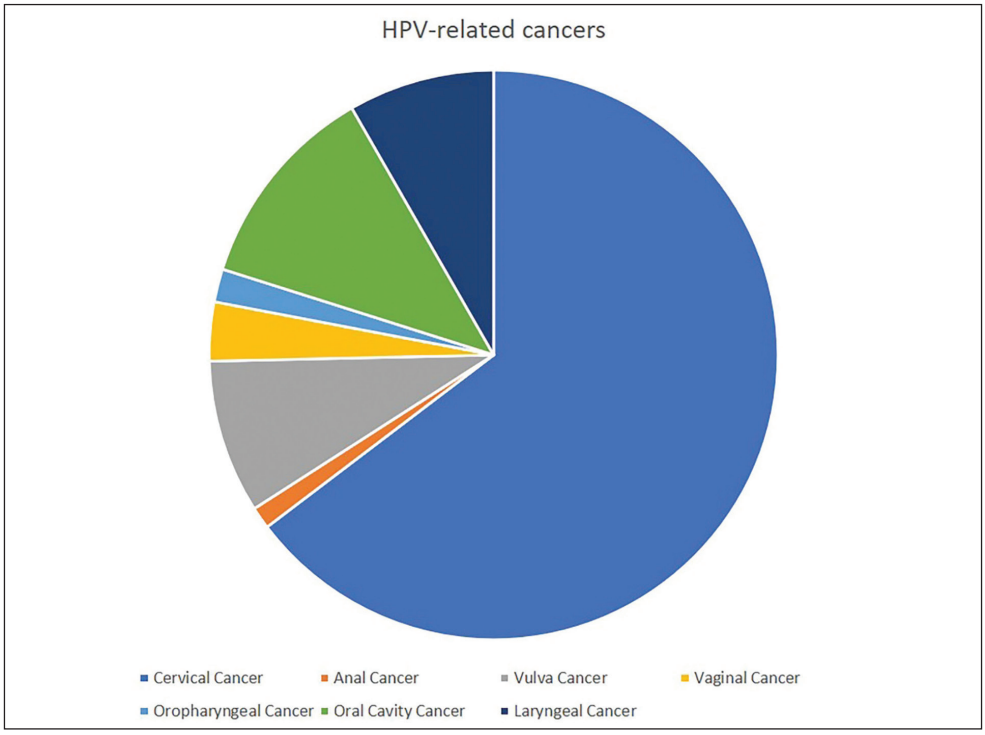

Figure 1. The frequency and distribution of HPV-related cancers in Bosnia and Herzegovina (adapted from: https://hpvcentre.net/statistics/reports/BIH_FS.pdf).

According to available data, cervical screening through the Pap test is widely accessible in 98% of surveyed institutions in BH (10). However, only 26% of these institutions have documented written protocols for conducting Pap tests. HPV testing is currently limited to specific regions of BH, including Tuzla, Sarajevo, and Banja Luka. Despite the HPV vaccine registration in BH since 2007, its role in cervical cancer prevention was not formally recognized until the 2011 Federation of Bosnia and Herzegovina (FBiH) health strategy (11). Despite this acknowledgment, a nationwide HPV vaccination program remains absent. Furthermore, comprehensive data on HPV prevalence within the general population in BH is currently unavailable (12). Beyond cervical cancer, a limited number of studies from BH explored and identified high-risk HPV subtypes in other cancers, such as head and neck, and colorectal cancers (13, 14).

We present a comprehensive review of the published literature and the current state of HPV-related cancers in BH. A thorough literature search revealed 23 studies on HPV prevalence and associated cancers in BH (Table 1) (9, 11, 13-33).

Table 1. Overview of Key Findings from HPV-Relevant Studies in Bosnia and Herzegovina

Authors	Cancer subtype	Participants (N)*	Age	HPV subtype	HPV (%)†	Most common HPV subtype (%)§	Detection method
Davies et al. 2023‡	Cervix	NA	NA	NA	NA	NA	NA
Davies et al. 2023‡	Cervix	NA	NA	NA	NA	NA	NA
Muhovic-Pasic et al. 2022	Cervix	375	NA	High-risk HPVs: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 Low-risk HPVs: 6, 11	2018: (54.43); 2019: (42.33); 2020: (39.08); 2021: (31.81)	HPV-16: 2018: (13.92); 2019: (11.04); 2020: (9.19); 2021: (13.03)	Multiplex PCR reaction
Gavrankapetanovic et al. 2022	NA	1517	Mean 33 (range 18 to 61)	High-risk HPVs: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68	(43)	HPV-16: (22.5)	Real-time PCR
Sadiković et al. 2020	Cervix	800	18 to 40	High-risk HPVs: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68	(33.5)	High-risk HPV: (33.5)	Hybrid capture II HPV test
Božić et al. 2020	Head and neck	50	NA	High-risk HPVs: 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68)	(22)	NA	Single PCR Nested PCR Real-time PCR
Jahic et al. 2020	Cervix	11051	NA	HPV 16,18,31, 35,39,45,51, 52,56,58,59, 66,68	NA	HPV-16: (50.5)	HPV in situ hybridization HPV genotypes 14 Real-TM Quant
Al-Thawadi et al. 2020	Head and neck	98 of 123 had interpretable results	Mean 62.8	High-risk HPVs: 16, 18, 31, 33, 35, 45, 51, 52, 58	(50)	HPV-18: (56)	PCR IHC
Gupta et al. 2020	Colorectal (96% rectal cancer)	106	Mean 65 (range 41 to 86)	High-risk HPVs: 16, 31, 18, 51, 52, 45	(80)	HPV-16: (53)	PCR IHC
Salimović-Bešić et al. 2019	Cervix	105	Average: Younger group 26.2; Range 19-30 Older group 40.9; Range 31-62	High-risk HPVs: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59	HPV DNA test: Younger group (83.9); Older group (67.6) DNA and mRNA test: Younger group (75.8) Older group (83.9)	HPV-16 in women aged ≤30 years: DNA test (32.1); mRNA test (26.4) HPV-16 in women aged >30 years: DNA test (33.0); mRNA test (29.8)	Real-time PCR amplification (HPV High Risk Typing Real-TM test) RNA-based assay: Real-time NASBA reactions

Continuation of Table 1

Authors	Cancer subtype	Participants (N)*	Age	HPV subtype	HPV (%)†	Most common HPV subtype (%)§	Detection method
Jahić et al. 2017	Cervix	3244	Average 41	High-risk HPV	NA	High-risk HPV in women with ASCUS (51); LSIL (71);	NA
Radić et al. 2017	Cervix	101	NA	HPV types: 11, 16, 18, 31, 35	(17.7)	HPV-16: (35.3)	Multiplex PCR
Jahić et al. 2016	Cervix	1784	Average 37.6	High-risk HPV	NA	High-risk HPV in women with ASCUS (51); CIN 1 (88)	In situ by hybridization
Salimović-Bešić et al. 2015	Cervix	105	Average 36.6	High-risk HPVs: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 Probable high- risk HPVs: 53, 66 Low-risk HPV: 70	(50.4)	HPV-16: (32.6)	Multiplex real-time PCR test
Iljazović et al. 2014	Cervix	283	Mean 51.7	High-risk and low-risk HPVs: 6, 11, 16, 18, 31, 33, 34, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 56, 58, 59, 66, 68, 70, 74	(94.7)	HPV-16: (95.5)	SPF-10 broad spectrum primers followed by deoxyribonucleic acid enzyme immunoassay and genotyping by reverse line probe assay (LiPA25, version 1)
Asotic et al. 2014	Cervix	6376	NA	NA	NA	HPV positive: CIN I (43.10); CIN II (27.93); CIN III (25.69); CIS (0.52); Normal findings (2.76)	PCR
Salimović-Bešić et al. 2013	Cervix	105	Average 31.6	High-risk HPVs: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59	(72.4%	HPV-16 in ASCUS (20.8); LSIL (30.6); HSIL (48.9)	HPV typing: multiplex real-time PCR mRNA typing: real-time NASBA assay
Poljak et al. 2013‡	Cervix	NA	NA	NA	NA	NA	NA
Bray et al. 2013‡	Anogenital, Head and neck	NA	NA	NA	NA	NA	NA
Seme et al. 2013‡	Cervix	NA	NA	NA	NA	NA	NA
Jahic et al. 2013	NA	100	35.7	High-risk and low-risk HPVs	NA	HPV positive in: LSIL (46); HSIL (48.9); normal Pap test (14)	Digene HPV test, Hybrid capture
Salimović-Besic et al. 2007	Cervix	148	NA	HPVs: 6, 44, 53, 66, 68, 72, 73	NA	NA	Hybrid Capture 2 HPV DNA PCR-PGMY11/ PGMY09 PCR-CPI/CPIIG
Iljazović et al. 2006	Cervix	55	NA	NA	NA	High-risk HPV after three months of therapy: (71.4)	Digene HPV Test-Hybrid Capture II

*Tested; †Prevalence; ‡Positive; §Prevalence. These studies address HPV-related cancer in Bosnia and Herzegovina but do not provide specific data regarding HPV positivity and HPV prevalence; HPV=Human papillomavirus; NA=Not applicable; PCR=Polymerase chain reaction; DNA=Deoxyribonucleotide acid; IHC=Immunohistochemistry; NASBA=Nucleic acid sequence-based amplification assay; ASCUS=Atypical squamous cells of undetermined significance; LSIL=Low-grade squamous intraepithelial lesion; HSIL=High-grade squamous intraepithelial lesion; CIN=Cervical intraepithelial neoplasia; CIS=Carcinoma in situ.

Cervical Cancer

Pathogenesis, Progression, and Types of Cervical Cancer

Cervical cancer develops due to persistent infection with high-risk HPV types, particularly HPV-16 and HPV-18 (34). HPV evades the host immune system by downregulating immune responses, allowing the infected cells to persist and proliferate (35). The mechanism by which is this happening is the virus entry in the basal cells of the cervical epithelium through micro-abrasions, following genome integration into the host DNA (36). This integration leads to the overexpression of viral oncogenes E6 and E7, which are central to the pathogenesis of cervical cancer. The E6 protein binds to and degrades the tumor suppressor protein p53, preventing the normal process of apoptosis and allowing cells with damaged DNA to survive and proliferate (37). Simultaneously, the E7 protein inactivates the retinoblastoma protein (pRb), leading to uncontrolled cell cycle progression and increased cellular proliferation (38). Persistent chronic inflammation due to the infection creates a microenvironment conducive to cancer development, with inflammatory cytokines and reactive oxygen species inducing DNA damage (37, 38). In advanced stages, it can metastasize to distant organs such as the lungs, liver, and bones (39). Clinically, early-stage disease may be asymptomatic or present with nonspecific symptoms like abnormal vaginal bleeding or discharge (37-39). The two primary types of cervical cancer are squamous cell carcinoma (SCC) and adenocarcinoma, accounting for 69% and 25% of all cases. The remaining ~6% include small cell (neuroendocrine) carcinoma (SCNC), primary cervical lymphomas, and soft tissue tumors, such as rhabdomyosarcoma (40-42). SCC typically progresses through a series of precancerous stages, known as cervical intraepithelial neoplasia (CIN). Screening methods such as the Pap test and HPV DNA testing play a critical role in detecting these precancerous changes, allowing for early intervention and reducing the risk of progression to invasive cancer (43). The treatment for SCC often involves surgical intervention, especially in the early stages, which may include conization, hysterectomy, or trachelectomy. In more advanced cases, radiation therapy, chemotherapy, or a combination of both is commonly employed. A literature search identified a single study on the treatment of cervical cancer in BH.

This study reported promising outcomes for inoperable locally advanced cervical cancer treated with chemobrachyradiotherapy. The treatment included external radiotherapy, concurrent low-dose brachytherapy with cisplatin and ifosfamide, and consolidation treatment with the same chemotherapy. The five-year local control rate was 94%, disease-free survival was 72.8%, overall survival was 76.6%, disease-specific survival was 88% and toxicity was acceptable (44). The outcomes of this study were similar to those reported in the original study by Vrdoljak et al., which used an identical protocol (45). Recent advances in targeted therapies and immunotherapies are also being explored, particularly in recurrent or metastatic SCC, showing potential in improving patient outcomes (46, 47). Adenocarcinoma constitutes about 25% of all cervical cancer cases and originates from the glandular epithelial cells lining the endocervix. Unlike SCC, adenocarcinoma arises from the mucus-producing cells and has distinct pathological and clinical features. This subtype is also strongly linked to HPV infection, particularly HPV 18, but it tends to be more challenging to detect through conventional Pap smears because the glandular cells are located higher up in the cervix, often beyond the reach of standard sampling techniques (48, 49). Histologically, adenocarcinoma can be further subclassified into several subtypes among which endocervical adenocarcinoma is the most common (49, 50).

The clinical management of adenocarcinoma mirrors that of SCC, with early-stage disease often treated surgically and advanced disease requiring chemoradiation. However, due to its unique biology and the challenges associated with its detection, adenocarcinoma often necessitates more specialized diagnostic and therapeutic approaches (51). SCNC is a rare but highly aggressive form of cervical cancer, characterized by small, round cells

that resemble those seen in small-cell lung cancer (52). It is associated with a poor prognosis due to its rapid growth and high likelihood of metastasis. SCNC is also linked to HPV infection, particularly HPV 18. Treatment typically involves a combination of surgery, chemotherapy, and radiotherapy, but outcomes remain poor (53). Recent molecular studies provide some opportunities for targeted treatments, given that a subset of SCNCs may harbor PIK3CA/PTEN/AKT and programmed cell death protein 1/PD-L1 alterations (52).

Epidemiology of Cervical Cancer in BH

Cervical cancer represents a significant public health problem in BH, as in many other countries. The incidence is generally lower than in other regions, but it remains a concern. According to the data reported by the Institute of Public Health of the FBiH, which represents approximately 70% of the total population of BH, in 2020 cervical cancer was the fifth most diagnosed cancer in women with a crude incidence of 10.0/100,000 women (54). With 67 registered deaths in 2020, cervical cancer was the 10th leading cause of cancer-related death in women. In BH, much of the available data relies on estimates from neighboring countries and reports from the World Health Organization (WHO) and the Catalan Institute of Oncology (ICO)/International Agency for Research on Cancer (IARC) (7, 55).

Current estimates by the HPV Information Centre indicate that there are about 312 new cases of cervical cancer diagnosed in BH annually, which ranks cervical cancer as the 6th most frequent female cancer in this country. According to these estimations, 153 women die from cervical cancer every year, which places cervical cancer as the ninth leading cause of cancer deaths in BH (56). As reported by GLOBOCAN 2022, the estimated age-standardized rates (ASR) for cervical cancer are 14.1 per 100,000 for incidence and 7.1 per 100,000 for mortality (57), which is less than reported in 2018, when the age-standardized incidence rate was estimated at 23.9/100,000, with an age-standardized mortality rate of 7.9/100,000 (58).

There is much inconsistency in the available data regarding the epidemiology of cervical cancer in BH, which is mainly the result of irregular reporting of newly diagnosed cases, but also due to the high burden of the health care system, deficiency of health care workers and the lack of infrastructure for efficient, reliable and timely health information system (59). The latest study investigating the epidemiology of cervical cancer in BH was published ten years ago, where the reported crude incidence in Tuzla Canton varied from 18.5 in 2005 to 4.8/100,000 in 2000 (55).

Comparison with Global and Regional Statistics

Cervical cancer is the most common HPV-related malignancy in the female population, as shown in Figure 1. Women at risk for cervical cancer (Female population aged >=15 yrs) is roughly estimated to be 1.41 million. According to the estimates, the overall cancer incidence rate is 218.6 cases per 100,000 persons per year. According to GLOBOCAN, in 2022 cervical cancer was the fourth most common cancer in terms of both incidence and mortality in women worldwide, with an estimated 660,000 new cases and 350,000 deaths. It is the most diagnosed cancer in 25 countries and the leading cause of cancer death in 37 countries (57). Survival rates for cervical cancer often vary according to a country's level of development. Around 84% of cervical cancer cases and 88% of related deaths occur in developing countries (60). In contrast, among developed nations, the five-year survival rates are much higher. In the United States, the five-year survival rate is 91% for localized disease, 60% for regional disease, and 19% for metastatic disease. Similar data are reported in the United Kingdom, with a five-year survival rate of 95% for stage I, 70% for stage II, 40% for stage III, and 15% for stage IV (61, 62). There are large disparities in incidence and mortality between different countries, with about a 10-fold variation, the highest rates being recorded in Eastern Africa (incidence 40.4/100,000 and mortality 28.9/100,000) and the lowest rates found in Western Asia (incidence 4.1/100,000 and mortality 2.2/100,000)

(57). Variance is also present between different European regions, with an age-standardized incidence rate of 15.7, mortality of 6.3/100,000 in Eastern Europe, and an incidence of 6.4 and mortality of 2.2/100,000 in Southern Europe. This is probably due to the different prevalence of chronic HPV infections and limited access to screening and vaccination in developing countries.

In the Summary Report published by the ICO/IARC Information Centre on HPV and Cancer, there were 58,169 new cervical cancer cases annually in Europe (estimations for 2020), which ranks cervical cancer as the 9th leading cause of female cancer and the 3rd most common female cancer in women aged 15 to 44 years in Europe. There are huge variations between different European regions and countries, with the highest age-standardized incidence rate of cervical cancer cases attributable to HPV recorded in Montenegro (26.2/100.000 women), Romania (22.6/100,000), Serbia and Lithuania (18.7/100,000) and the lowest in Switzerland (3.4/100,000), Malta (3.7/100,000), Luxembourg and Finland (5.2/100,000). Compared to other European countries, BH is ranked 11th with 14.3 per 100,000 women (56). In Croatia, where organized screening has been present since 2012, the age-standardized incidence rate is estimated at 10.1 per 100,000 women. In Croatia, the incidence is still relatively high, with 276 cases annually (ASR 11.0/100,000), as is the mortality (ASR 4.2/100,000) (63). The age-standardized mortality rates per 100,000 women per year in BH are 5.2, while in Serbia, Croatia, and Montenegro, the rates are estimated at 7.9, 3.2, and 10.5, respectively (56).

Local Risk Factors for Cervical Cancer

Cervical cancer represents 1.8% of all cancer cases, with a corresponding mortality rate of 1.8% (7). In the 2014 analysis, most cases (92.2%) were histologically classified as SCC, and 95% tested positive for HPV. Infections were predominantly single, accounting for 95.5% of cases, with HPV-16 and 18 being the most prevalent, responsible for 77.8% of the positive cases. Other notable HPV types included HPV-45 (4.4%), HPV-33 (3.1%), HPV-51 (2.3%), and HPV-31 (2.2%). The mean age of individuals infected with the seven most common HPV types globally HPV-16, HPV-18, HPV-45, HPV-31, HPV-33, HPV-52, and HPV-58—was 51.1 years (with a standard deviation of 11.6 years). This is notably younger by six years compared to individuals infected with other HPV types, whose mean age was 56.3 years (with a standard deviation of 12.9 years) (11). Various reports from BH indicate a prevalence of cervical HPV infection ranging from 17% to 72% (Table 1) (9, 17, 20-23, 25, 26, 30-33). The five studies listed in Table 1 explored HPV-related cancer in BH but lacked specific information on HPV positivity and prevalence specific to the country (15, 16, 27-29). Furthermore, the data from these studies primarily reflected HPV status across Central and Eastern Europe.

In BH, various risk factors contribute to the prevalence of HPV infections and related cancers, particularly cervical cancer. These factors are shaped by socioeconomic challenges, cultural norms, and a fragmented healthcare system. One significant issue is the limited access to healthcare services, including regular cervical cancer screenings and HPV vaccinations. Socioeconomic disparities further compound this issue, as poverty and economic instability limit access to healthcare. Many individuals, particularly from low-income backgrounds, may not prioritize or afford preventive measures, such as screenings and vaccinations. Additionally, educational barriers and a lack of awareness about HPV contribute to high-risk behaviors and delayed diagnosis (64, 65). Cultural and social norms also influence HPV risk factors. Sexual behaviors, such as early initiation of sexual activity, multiple sexual partners, and inconsistent condom use, are associated with increased HPV transmission. In BH, cultural stigmas surrounding sexual health may limit open discussions and reduce awareness about protective measures. Traditional gender roles may further restrict women's access to preventive care and hinder their ability to discuss HPV-related concerns with healthcare providers. The fragmented healthcare

infrastructure in the country presents another challenge. Under-resourced and disjointed, the healthcare system struggles to implement comprehensive HPV prevention and treatment programs. This fragmentation hampers efforts to accurately assess the burden of HPV-related diseases and target interventions effectively (55). Additional risk factors include smoking and co-infections. Smoking is a known co-factor that can exacerbate the risk of HPV-related cancers, particularly cervical cancer, and its prevalence in BH may contribute to higher cancer rates among HPV-infected individuals (66). Up to 41% of adults in BH consume cigarettes (67). Other factors, such as co-infections with other sexually transmitted infections, such as chlamydia, also increase the risk of HPV persistence and progression to cancer, further compounded by limited sexual health education and resources (68).

Other HPV-Related Cancers

Vulvar Cancer: Epidemiology, Risk Factors, and Treatment

Vulvar cancer is the twenty-ninth most prevalent cancer in women worldwide, with around 47,342 new cases reported in 2022 (57). In Europe, it represents the nineteenth most common cause of cancer incidence in women with approximately 16,506 new cases in 2020 (69). According to data from the SEER database, five-year survival rates vary by stage: 85.6% for localized disease (stages I/II), 47.5% for regional or locally advanced disease (stages III/IVA), and 23.3% for stage IVB, which encompasses patients with pelvic nodal involvement (70). In geographic terms, there is around a 30-fold variation in the recorded incidence rates of vulvar cancer with the higher incidence in seven countries and three continents, amongst them Bahrain, Germany, the Netherlands, Canada, France, Australia, and the United Kingdom (71, 72). The incidence rates of vulvar cancer are approximately 2-fold higher in high-income countries (ASR = 1.56 per 100,000) than in low- and middle-income countries (ASR = 0.6 per 100,000), while the difference in mortality rates is less pronounced (ASR = 0.35 vs ASR = 0.27) (73). In Central and Eastern Europe and Central Asia, vulvar cancer incidence and mortality rates are 2-3 times higher than other anogenital cancer sites (28). The estimated age-standardized incidence in Europe is 1.68/100,000 women with a mortality rate of 0.51/100,000. The highest incidence in Europe is recorded in Germany, with an ASR of 3.61/100.000 and a mortality rate of 0.71. According to National Cancer Registry data, around 350 new cases of vulvar cancer are diagnosed in Poland each year, with 200 women dying from the disease (74). Croatia ranked tenth among EU-27 nations for age-standardized vulvar cancer incidence in 2022 and second in terms of vulvar cancer fatality estimates. Eastern Europe (Slovakia, Romania, Hungary, and Poland) had the highest fatality rates for vulvar cancer, with Germany ranking fourth (75). According to the Croatian National Cancer Registry data, 1451 women were diagnosed with invasive vulvar cancer and 814 women died due a vulvar cancer in the period 2011-2019. In BH, an estimated number of new cases of vulvar cancer for 2020 was 42 (76). The incidence is estimated at 1.06 and mortality at 0.57/100,000, which is lower than in Croatia and Serbia, where the estimated incidence is 1,67 for both countries and mortality at 0.54 and 0.69, respectively. Montenegro has the highest estimated mortality rate (0,90/100,000) in Europe, while the incidence rate of 1.36/100,000 is similar to other countries in the region (56).

The epidemiology disparities between different countries and regions are most likely a result of the availability of screening programs since the detection of vulvar cancer is linked to screening for cervical cancer. Another factor could also be the lack of public awareness, social, religious, and cultural differences, but also the lack of national cancer registries and adequate reporting of new cases (72).

Vulvar cancer primarily affects elderly women. More than 60% are keratinizing vulvar SCC (VSCC), followed by the basaloid type which is more common in young women and linked mostly to HPV-16 (72, 77, 78). Age, the presence of HPV, tobacco use, HIV infection, vulvar

intraepithelial neoplasia, and lichen sclerosus are the most common risk factors for vulvar cancer (77). As previously mentioned, basaloid carcinomas are more likely to be HPV-positive than keratinizing carcinomas. They share HPV-related factors with cervical cancer, such as lifetime sexual partners, age at first intercourse, and cigarette smoking. However, their etiologies differ (71). 30-60% of VSCCs are HPV related with significant variation across studies (78, 79). According to WHO 2020 classification, ESGO, and NCCN guidelines, it is mandatory to stratify VSCC into HPV-associated and HPV-independent using p16 immunohistochemistry (77, 80, 81). In addition, HPV-independent VSCC is divided into two categories: p53 mutant (p53mut) and p53 wild-type (p53wt), and therefore it is recommended to assess p53 status according to NCCN and ESGO guidelines for the proper management of patients with VSCC (77, 80). There is growing evidence that HPV-associated and p53wt cancers may have a better prognosis than those p53mut. Among retrospectively analyzed 413 samples of VSCC, the 5-year overall survival was 83% for HPVpos VSCC, 64% for HPVneg/p53wt VSCC, and 48% for HPVneg/p53mut VSCC. Women with HPVpos VSCC were younger at surgery (59 years) than those with HPVneg/p53wt VSCC or HPVneg/p53mut VSCC (73 and 75 years, respectively). The majority of patients with HPVpos VSCC (79%) or HPVneg/p53wt VSCC (81%) tumors had stage I/II disease, contrary to (57%) HPVneg/p53mut VSCC (Table 2) (82). In addition, a meta-analysis evaluating 18 studies, including 475 women with VSCC, reported that HPV-associated VSCC showed a significant correlation between p16pos/p16neg and overall survival (ranging from 62% to 81% vs 22% to 47% in 5-year OS).

Among them, four studies in this meta-analysis reported an overall survival according to p53, including 310 women with VSCC of which 166 (53.5%) were p53 positive and 144 were p53 negative. Women with p53 positive VSCC had a significantly worse 5-year OS (ranging from 35-63%) compared to p53 negative (ranging from 68-70%) (Table 2) (83). In the era of personalized medicine, a potential strategy to tackle high operation morbidity and pre-operative risk assessment based on the molecular subtype of VSCC is valuable in tailoring surgery, patient counseling, and planning adjuvant treatment for the patient's risk profile. A single study's findings revealed that the concordance of preoperative and postoperative molecular subtypes in a relatively small number (N=57) of samples was 91.2%. These findings could assist in therapy tailoring, particularly given the less aggressive behavior of HPV-associated VSCC and the fact that these cancers occur in younger

Table 2. Overview of the Relevant Studies Examining the Survival of Patients with HPV-Related Cancers According to p16, p53, and HPV Status

Author	Tumor type	Tested patients (N)	HPV Subtype(s)	Molecular subtype	OS (%)	Detection method
Kortekas et al.	Vulva	413 75 275 63	HPV-16, 18, 33	HPVpos HPV neg/p53mut HPV neg/p53wt	5y OS (83) (48) (64)	IHC
Sand et al.	Vulva	475 181 294 310 166 144	NA	p16pos p16neg p53pos p53neg	5y OS range (62-81) (22-47) 5y OS range (35-63) (68-70)	IHC
Feldbaum et al.	Vagina	43	NA	p16pos p16neg	Mean 49.5 months 25.3 months	IHC

OS=Overall survival; IHC=Immunohistochemistry; ISH=In-situ hybridization; HPV=Human papillomavirus; RNA=Ribonucleic acid; DNA=Deoxyribonucleotide acid; PCR=Polymerase chain reaction; NA=Not applicable.

women. On the contrary, in older and frail patients unfit for upfront surgery, in the light of recently published studies, definitive or neoadjuvant chemoradiotherapy or chemotherapy, which have shown durable responses, could also be an option (84-86). Comprehensive genomic profiling among HPV-associated and HPV-independent VSCC showed two distinct entities (87). HPV-positive VSCC exhibited PI3K/mTOR pathway mutations and was enriched in *FGFR3* and *PTEN* mutations (87, 88). In a cohort of HPVpos VSCC, 61% of tumors had genetic mutations in the PI3K/mTOR pathway. HPV-positive cancers sequenced from metastases had a significantly greater rate of *STK11* mutations, a negative regulator of mTOR signaling, than HPV-positive tumors sequenced from primary cancer (88). Depending on the stromal invasion, local treatment is recommended, or a wide local excision (T1a ≤1 mm of stromal invasion) or a radical partial vulvectomy (T1b >1 mm of stromal invasion), especially in cases with multifocal involvement, to obtain surgically negative margins (according to recent guidelines, a pathological minimal margin of >2-3 mm seems adequate). Groin treatment should be performed for tumors greater than T1a and could be performed in various ways depending on the tumor size and distance from midline; radical partial vulvectomy and ipsilateral inguinofemoral lymphadenectomy with or without sentinel lymph node biopsy or radical partial vulvectomy and bilateral inguinofemoral lymphadenectomy or a sentinel lymph node biopsy in selected cases. Adjuvant treatment (radiotherapy or chemoradiotherapy) is advised for patients with a positive margin and lymph node involvement. In patients with locally advanced inoperable VSCC, primary chemoradiotherapy or neoadjuvant platinum-based chemotherapy is recommended after a thorough multidisciplinary assessment in selected cases (77, 80). Systemic therapy, platinum-based chemotherapy, is recommended in a metastatic setting or recurrent, inoperable disease. In the post-progression setting, there are no standard treatments, although chemotherapy, VEGF inhibitors, immune checkpoint inhibitors, EGFR inhibitors, or, in the case of a *NTRK1-3*-positive tumor, larotrectinib or entrectinib, could be considered (77, 80, 89, 90). New promising approaches to the treatment of HPV-related cancers include adaptive T cell therapy (clinical trial NCT01585428, in which two of nine patients with metastatic cervical cancer had complete responses), cancer vaccines (ISA101, a peptide vaccine developed for HPV-related cancers), and intra-tumoral oncolytic viral therapy (79). A clinical trial using a T cell receptor that targets the E7 antigen is currently enrolling patients (NCT02858310) (91).

Vaginal Cancer: Epidemiology, Risk Factors, and Treatment

Primary vaginal cancer accounts for only 2% of female genital tract cancers in adulthood, with an estimated incidence of 18,800 new cases diagnosed worldwide in 2022 (57, 92). A report using population-based cancer registries found a threefold variance in recorded incidence rates for vaginal cancer. However, vaginal cancer incidence was lower and more stable than vulvar cancer, despite the larger HPV-attributable fraction among cohorts born 1940-50 and afterward. The Dominican Republic has the highest risk of vaginal cancer (ASR=2.7 per 100,000), followed by Malawi and Zambia, with rates of 1.4 and 1.3 per 100,000, respectively (71). According to GLOBOCAN, vaginal cancer ranks 33rd worldwide in terms of both incidence and mortality. The age-standardized rate (ASR) for incidence is 0.36 per 100,000, while the ASR for mortality is 0.15 per 100,000 (57). In Europe, the ASR of vaginal cancer incidence for 2020 is estimated to be 0.33 per 100,000, with the highest rates observed in Northern Europe at 0.38 per 100,000. An estimated number of new cases of vaginal cancer for 2020 in BH was 14 (93). The incidence is estimated at 0.41 per 100,000, which is higher than the rates in Croatia and Serbia, both of which have an incidence rate of 0.33 per 100,000. Conversely, Montenegro has the highest estimated incidence rates in Europe, with an ASR of 0.74 per 100,000 women (56). These data are comparable to those observed for cervical cancer, likely

attributable to the prevalence of chronic HPV infection, which is a major risk factor for both cervical and vaginal carcinoma. In adults, only 10% are vaginal-originating cancers, whereas the rest are spread from other locations such as the cervix, endometrial, vulva, and rectum (94). The majority of primary vaginal SCC cases are HPV-associated (Table 3); thus, the risk factors for vaginal SCC are the same as those for cervical cancer: multiple lifetime sexual partners, early age at first intercourse, and smoking. A history of vaginal adenosis [related or not to diethylstilbestrol (DES)] is another risk factor for some kinds of adenocarcinoma, as is past DES exposure and endometriosis (92). Individuals with AFAB (hysterectomized individuals assigned female at birth) and pre-existing cervical intraepithelial neoplasia are more than twice as likely to develop vaginal cancer (95). SCC is the most frequent histologic type accounting for ~90% of cases (92, 95). Persistent infection with high-risk HPVs has been found in vaginal malignancies, as well as 85-90% of vaginal intraepithelial neoplasia grades 2 and 3 (VaIN2). The most frequent form, HPV-16, is seen in 46-77% of vaginal malignancies. HPV-18 has been detected in lower percentages (78, 96).

Primary vaginal adenocarcinomas are very uncommon, while other morphologic subtypes are rarer (92, 95). In 2020, the WHO modified the categorization of female genital tumors and recommended a distinction between HPV-associated and HPV-independent vaginal SCC (81). A retrospective assessment of 43 vaginal cancer patients found that those with p16- positive diffuse staining had a significantly higher survival rate (~50 months) compared to those with p16-negative disease (~25 months) (Table 2) (97). The most important prognostic factors for vaginal cancer are the stage at diagnosis, tumor size greater than 4 cm, age, and tumor position outside of the upper region of the vagina. Adenocarcinoma has a worse prognosis than squamous cell carcinoma (98, 99). Patients with vaginal cancer are often treated with radiation, surgery, chemoradiation, or a combination of these treatments, regardless of their cancer subtype and HPV infection status. Treatment options differ by stage (92, 95). There are two options for early curative management: surgical excision (with microscopically clear margins without unnecessary morbidity) or chemotherapy and radiation therapy. Primary chemoradiotherapy involves external beam radiation (EBRT), brachytherapy, and cisplatin-based chemotherapy as the recommended protocol for stages II-IVA disease. Cisplatin-based chemotherapy should be administered concurrently. When cisplatin is not an option for vaginal cancer treatment, carboplatin or radiotherapy may be used instead. Premenopausal women should be informed about ovarian transposition early on (92, 98). For patients with limited distant (oligo-) metastatic disease at presentation, curative treatment options include stereotactic radiation, surgery, and radiofrequency ablation. Because vaginal cancer is a rare entity and similar to cervical cancer, treatment decisions are often based on cervical cancer guidelines. According to current guidelines for metastatic disease next-generation sequencing (NGS) and comprehensive molecular profiling are recommended. The following biomarkers should be tested: PD-L1, tumor mutational burden (TMB), p53, *RET* fusion, MSI-H, *NTRK1-3* fusions, and HER2 (95). The current standard of care for PD-L1 positive metastatic disease is a combination of cisplatin-based chemotherapy and pembrolizumab with or without bevacizumab, based on the results of KEYNOTE-826 study that revealed a statistically significant improvement in PFS, OS, and ORR (100). The addition of pembrolizumab to chemotherapy with or without bevacizumab continued to show significant survival benefits in PD-L1-positive tumors at a median follow-up of 39.1 months, with a median OS and PFS of 28.6 and 10.5 months versus 16.5 and 8.2 months in the pembrolizumab plus chemotherapy arm versus the placebo plus chemotherapy arm (101). Otherwise, based on the GOG-240 study, adding bevacizumab to cisplatin-based chemotherapy in the first-line setting of metastatic, persistent, or recurrent cervical cancer resulted in a substantial improvement in OS among patients receiving bevacizumab, especially in patients who were not treated with prior pelvic radiotherapy (102). Additional therapy options in

Table 3. Overview of the Representative Studies Reporting HPV Prevalence in HPV-Related Cancers

Author	Tumor type	Tested participants (N)	Age	HPV subtype	HPV positive (%)	Most common HPV subtype (%)*	Detection method
Komloš et al. 2011	Anal (invasive and in situ)	21	NA	High-risk and low-risk HPV; 6, 16, 52, 61	95.8	HPV-16 (90.5)	GP5+/6+ PCR / Inno-LiPA
Tachezy et al. 2007	Anal squamous cell carcinoma	22	Mean = 64.2; Range 47-86	High-risk HPV 16	81.8	HPV-16 (81.8)	GP5+/6+ PCR / RLB and sequencing
De Vuyst et al. 2009	Anal (29 studies)	955	NA	HPV-18 HPV-33	84.3	HPV-16 (73.4)	PCR
	Vaginal (14 studies)	136	NA	HPV-18 HPV-31	69.9	HPV-16 (53.7)	
	Vulvar (63 studies)	1,873	NA	HPV-33 HPV-18 HPV-6 HPV-11	40.4	HPV-16 (32.3)	
Frisch et al. 1997	Anal (invasive and in situ)	388	Median = 63; Range 26-94	High-risk HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 Low-risk HPV, 6, 11, 40, 42, 43, 44	84	HPV-16 (73.4)	PCR
Škamperle et al. 2013	Anal (3 studies)	43	NA	HPV-16, HPV-6, HPV-52, HPV-61	Overall HPV DNA prevalence = 90.7	HPV-16 (94.9)	PCR (MY09/11 / DBH and sequencing GP5+/6+ PCR / RLB and sequencing HPV-16/18 TS PCR and Linear Array® MY09/11 / HPV-16 TS PCR and sequencing HPV-16/18 TS PCR MY09/11 PCR / RFLP MY09/11 PCR / pU-1M/2R PCR GP5+/6+ PCR / IA and RLB Inno-LiPA® MY09/11 PCR / HPV-16/18 TS PCR HPV-16, -18, -33 TS PCR E6-E7 consensus PCR / HPV-16, -18, -31, -33, -45, -52, -59, -68 TS PCR)
	Cervical (24 studies)	2,531	Mean 50.2	HPV-16, HPV-18, HPV-31, HPV-33, HPV-45, HPV-35, HPV-39, HPV-51, HPV-52, HPV-56, HPV-58, HPV-59, HPV-68	Overall HPV DNA prevalence= 86.6	(59.6)	
	Vulvar (3 studies)	164	NA	HPV-16, HPV-33, HPV-45, HPV-58, HPV-6, HPV-42	Overall HPV DNA prevalence= 32.9	(22)	
Šimić et al. 2023	Oral cavity, oropharynx	76	Median= 61	High-risk HPV 16, 18	23.7	HPV-16 (77.7)	PCR

*Prevalence. Inno-LiPA®=INNO-LiPA HPV Genotyping Extra test (Innogenetics NV, Ghent, Belgium) or INNO-LiPA HPV genotyping test (Labo Biomedical Products, Rijswijk, the Netherlands); Linear Array®=Linear Array® HPV genotyping test (Roche Molecular Systems Inc., Alameda, CA, USA); PCR=Polymerase chain reaction; TS PCR=Type-specific PCR; DBH=Dot-blot hybridization, RLB=Reverse line-blot hybridization; IA=Immuno-assay–enzyme-linked oligosorbent assay; NA=Not applicable; HPV=Human papillomavirus; DNA=Deoxyribonucleotide acid.

subsequent lines include chemotherapy, immune checkpoint inhibitors (pembrolizumab, cemiplimab, nivolumab), biomarker-specific therapies based on agnostic tumor approvals (trastuzumab deruxtecan for HER2 positive tumors, selpercatinib for *RET* gene fusion-positive tumors, and TRK inhibitors for, *NTRK1-3* fusion-positive tumors) (103-109). Tisotumab vedotin (TV) is an

ADC (antibody-drug conjugate) that consists of an anti-TF (tissue factor) monoclonal antibody covalently linked to the microtubule-disrupting agent MMAE via a protease-cleavable linker. It is FDA-approved for the treatment of recurrent or metastatic cervical cancer with disease progression on or after chemotherapy based on phase 3, randomized, innovaTV-301/ENGOT-cx12/GOG-3057 where patients receiving TV had a 30% reduction in risk of death versus chemotherapy (110). Ongoing developments in the management of locally advanced cervical cancer include the use of immune-checkpoint inhibitors with chemoradiotherapy (KEYNOTE-A18 study (NCT04221945), and in recurrent/metastatic cervical cancer, TV might be established as a first-line treatment (111, 112).

Anal Cancer: Epidemiology, Risk Factors, and Treatment

Anal cancer is a rare disease that accounts for <3% of all gastrointestinal cancers with an annual incidence of 0.5-2.0 in 100,000 (113). Five-year overall survival (OS) rate improved from a mean estimate of 64% in 1980 to 75% in 2010 (114). Based on GLOBOCAN 2020, anal cancer ranks 30th globally in terms of both incidence and mortality (69). In 2020, there were 54,194 new cases (23,999 males and 30,195 females) of anal cancer worldwide, involving the anal canal, or anorectum (57). However, there are varying reports indicating an increase in incidence among both men and women over the past 20 years, particularly in high-income countries (113, 115). According to IARC, the estimated age-standardized incidence rate for anal cancer in Europe for 2020 was 0.66/100,000 for men and 1.05/100,000 for women, with the highest incidence for men recorded in Germany (1.20/100,000) and for women in France (2.53/100,000). The incidence rate estimated for BH was 0.19 for women and 0.20 for men, which is lower in comparison with Croatia, Serbia, and Montenegro, where the rates were estimated at 0.27, 0.36, and 0.38 for women and 0.34, 0.55, and 0.77 for men, respectively. The estimated mortality rate in Europe was 0.24 for women and 0.22 for men, with the highest recorded in the Czech Republic for both women (0.42/100,000) and men (0.55/100,000). The mortality rate for BH is estimated at 0.12/100,000 for men and 0.08 for women, which is lower than in Serbia, where it was estimated at 0.29 for men and 0.14 for women (56). As reported by GLOBOCAN 2022, BH is one of the countries with the lowest ASR of incidence (0.16) and mortality (0.04) in Europe (57). However, these estimates have a high degree of uncertainty because they are not derived from population-based cancer registries.

SCC constitutes 80–85% of all anal cancers. Adenocarcinomas are the second most common type, accounting for 5–18% of all cases, and in that case, should be treated as low rectal cancers (116). Anal carcinoma has been associated with HPV infection (anogenital warts), a history of receptive anal intercourse or sexually transmitted diseases, a history of genital tract cancer, immunosuppression from solid organ transplantation, or HIV infection. In addition, other risk factors include smoking, autoimmune disorders, and hematologic malignancies (116, 117). However, persistent infection with high-risk HPV variants (e.g., HPV-16, HPV-18) is strongly linked to anal cancer (118, 119). The prevalence and distribution of HPV in anogenital cancers in 16 Central and Eastern European countries including BH ranged from 81.8% to 100% (120). Overall, 37 (94.9%) of 39 HPV DNA-positive anal malignancies from the Slovenian and Czech cohorts were positive for HPV-16 (120-123). Meta-analysis of anogenital cancerous and precancerous lesions found the highest HPV prevalence in anal cancer (84.3%), predominately HPV-16 (73.4%) (78). A large study of tumor specimens of anal cancer discovered a high prevalence of high-risk HPV DNA in 84% of anal cancer specimens, particularly HPV-16, which was detected in 73% of them (Table 3) (124). Contrary to that, high-risk HPV was not found in any of the rectal cancer tissues tested, although various reports lately have stated the potential link between HPV and EBV co-presence as a possible contributing element to colorectal cancer development (124, 125). Among them, a report on the Qatari population found the presence of high-risk HPV in 52%

of colorectal cancer samples, whereas coinfection with more HPV subtypes was strongly correlated with advanced-stage colorectal cancer (125, 126). In addition to that finding, the high prevalence of high-risk HPV types (HPV-16 and HPV-18) among colorectal cancer samples in the Bosnian population was ~50% (Table 1) (14). Further research is needed to more thoroughly evaluate the potential role of the presence of high-risk HPV in colorectal carcinogenesis. An early-stage perianal disease that does not affect the anal sphincter and superficially invasive SCC of the anus can be treated with local excision, where negative margin excision can be accomplished without compromise of the adjacent sphincter muscles.

Combined chemoradiotherapy is the primary therapeutic preference for locoregional anal cancer (127). Over the past four decades, the current standard of care has been the combined modality of 5-FU (capecitabine) and mitomycin with radiotherapy where intensity-modulated radiotherapy is the preferred modality over 3D-conformal radiotherapy, according to the results of the phase 2 RTOG trial, which showed significant reductions in hematological, dermatological, and gastrointestinal toxicity (127–130). A retrospective National Cancer Database review of 10,524 patients with nonmetastatic disease from 2004 to 2015 revealed no benefit to OS with a higher dose of radiation of 54-60 Gy compared to 54 Gy in locally advanced anal cancer (HR 1.08, P=0.166) (131). Current guidelines propose the suggested dose according to the RTOG-0529 trial (127, 130). Ongoing research in locally advanced anal cancer focuses on strategies to reduce radiation-associated toxicities, such as bone marrow-sparing IMRT (VMAT) and proton beam radiotherapy (132, 133). Immunotherapy is currently recommended as a second-line treatment for metastatic cancer; preferably with nivolumab or pembrolizumab based on the NCI9673 and Keynote-158 studies, regardless of PD-L1 status (127, 134, 135). A post-hoc analysis and retrospective analysis within the NCT02919969 and NCI9673 studies showed that patients with durable responses to immune checkpoint inhibitors had higher levels of tumor-infiltrating CD8+PD-1+T cells, PD-L1-positive tumors, and HPV positivity, based on p16 IHC (134, 136). Overall survival, locoregional recurrence, and disease-free survival were improved in HPV-positive SCC compared to HPV-negative SCC (137). Immunotherapy is also being investigated in locoregional settings, particularly in combination with radiation therapy, because of its potential role as a sensitizer for immune checkpoint inhibitors by increasing antigen presentation by dendritic cells (138) and tumor-infiltrating lymphocytes, especially in patients with a high HPV16 viral load (139). When patients are diagnosed, approximately 10% have metastatic disease, and those with localized disease treated with CRT have a ~10% likelihood of metastatic recurrence (140). According to the InterAACT trial, a combination of carboplatin and paclitaxel is currently the optimal frontline therapy option for metastatic squamous cell anal carcinoma and is listed as a preferred first-line option in current guidelines (127, 140). Immune checkpoint inhibitors are currently being explored in combination with chemotherapy in treatment-naïve metastatic anal cancer, triplet therapy with the HPV-16 vaccine, NHS-IL12 tumor-targeted immunocytokine, and M7824 bifunctional fusion protein targeting PD-L1 and TGFβ in metastatic or refractory/recurrent HPV-associated malignancies, or with the EGFR/TGFβ fusion monoclonal antibody in locally advanced/unresectable or metastatic, immune-checkpoint-naïve EGFR-driven advanced solid tumors (NCT04444921, NCT04287868, NCT04429542) (141-143). Mutations or amplifications of the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) are another possible target in HPV-positive SCC. Alterations in other cancer drivers, like FBXW7 and KMT2D, occur at a low frequency, typically ~10-20% within most cohorts (144).

Oropharyngeal Cancer: Epidemiology, Risk Factors, and Treatment

Head and neck cancers (HNC) involve the upper aerodigestive tract, including the oral cavity,

nasopharynx, oropharynx, hypopharynx, and larynx. Squamous cell carcinoma is the most prevalent histology (145). Head and neck squamous cell carcinoma as a combined entity (HNSCC) is the sixth most prevalent malignancy worldwide, with an incidence in both sexes >890,000 new cases in 2022 (57, 146, 147). HNC often gets diagnosed in the advanced stage with a 5-year survival rate of only 40-50% (148, 149). The primary risk factors for HNSCC development include smoking and heavy alcohol consumption. Recently, HPV has been linked to oropharyngeal cancers. Tobacco and alcohol-induced HNSCC is decreasing in Western countries, whereas HPV-driven HNSCC, particularly oropharyngeal, is increasing in young people, especially non-drinkers and non-smokers (146, 150, 151). According to GLOBOCAN 2022, oropharyngeal cancer is ranked 24th in terms of incidence and 23rd in terms of mortality globally (57). The age-standardized rates (ASR) for oropharyngeal cancer are estimated to be 1.1 per 100,000 for incidence and 0.53 per 100,000 for mortality. In the United States, the overall incidence of HPV-positive oropharyngeal cancers is rising, especially among men (152), whereas the incidence of HPV-negative oropharyngeal cancers, which are primarily associated with tobacco and alcohol use, is declining (153). In the United States and certain regions of the European Union, the attributable fraction of HPV in newly diagnosed oropharyngeal cancers is estimated to be 60-70% (154). Globally, oropharyngeal cancer occurs two to three times more often in men than in women. However, women worldwide have a higher rate of HNC associated with HPV than men for cancers of the oropharynx and larynx. Women were more likely to have oropharyngeal cancer associated with HPV than men in Central-Eastern Europe (61.5% vs. 45.5%), Southern Europe (22.6% vs. 8.4%), and Western Europe (38.9% vs. 13%), but not in Northern Europe (50% vs. 50%) (150). The ASR for oropharyngeal cancer incidence in women across Europe is estimated at 0.92 per 100,000, with the highest rate observed in Western Europe at 1.53 per 100,000. Denmark has the highest incidence in Europe, with an ASR of 2.58 per 100,000. In contrast, BH has a lower estimated ASR of 0.27 per 100,000 compared to Serbia (0.42), Croatia (0.36), Slovenia (1.0), and Montenegro (0.64). The incidence of oropharyngeal cancer is considerably higher in men, with an ASR estimated at 3.74 per 100,000 in Europe. Eastern Europe reports the highest rate, with an incidence of 4.36 per 100,000. Romania has the highest ASR for incidence in Europe at 8.0 per 100,000. In contrast, BH has lower rates, with an ASR of 1.42 per 100,000, similar to Montenegro (1.18 per 100,000). The incidence rates in other regional countries are somewhat higher, with ASRs estimated at 2.72 for Serbia, 2.62 for Croatia, and 6.54 per 100,000 for Slovenia. The estimated ASR for mortality from oropharyngeal cancer in women across Europe is 0.28 per 100,000, with the highest mortality observed in Western Europe at 0.40 per 100,000. Denmark and Hungary have the highest mortality rates in Europe, with an estimated ASR of 0.56 per 100,000. Montenegro also exhibits a high estimated mortality rate of 0.53 per 100,000. In contrast, BH has a relatively low mortality rate of 0.07 per 100,000, which is lower compared to regional countries such as Serbia (0.17), Croatia (0.21), and Slovenia (0.24). The estimated ASR for oropharyngeal cancer mortality in men across Europe is 1.70 per 100,000, with the highest rate recorded in Eastern Europe at 2.31 per 100,000. Moldova reports the highest mortality rate in Europe, with an ASR of 5.03 per 100,000. Among other regional countries, Slovenia and Croatia also exhibit higher mortality rates, with ASRs of 3.06 and 2.22 per 100,000, respectively. In contrast, BH has a lower mortality rate of 0.80 per 100,000, which is similar to the rate in Montenegro at 0.66 per 100,000 (56).

Most cases of HPV-associated HNSCC contain HPV-16, which can induce carcinogenesis through the expression of oncoproteins E6 and E7. These oncoproteins promote angiogenesis, genomic instability, telomere shortening inhibition, apoptosis suppression, and contribute to invasion and metastasis through interaction with tumor suppressor proteins p53 and pRb (3,155-157). While HPV-16 is the most frequent type, genotyping differs based on gender and geography; the global prevalence

ranges from 0 to 60% (11). In a small Croatian cohort, the results were consistent with previous studies, but in Bosnian HNSCC samples, the most commonly expressed high-risk HPVs were HPV-18, with HPV-16 ranking fourth (Tables 1 and 3) (3, 13, 158). A retrospective analysis of 50 patients from the University Clinical Center of Banja Luka found that HPV was present in 27.3% of oropharyngeal malignancies. High-risk HPVs were found in 22% of head and neck cancer samples (Table 1) (19). Oropharyngeal cancer is classified as either HPV positive with a better prognosis or HPV negative with a worse prognosis, although multicenter, multinational individual patient data analysis suggests that double testing with p16 and HPV should be performed because their findings provide robust evidence of discordance in HPV and p16 prevalence in these patients, which translates to overall survival. The median overall survival for p16+/HPV+ cases was 15 years, while p16-/HPV- cases had a median of 3.5 years, p16-/HPV+ cases had a median of 5.3 years, and p16+/HPV- cases had a median of 6.7 years. Overall 5-year survival rates were 81.1% for p16+/HPV+, 40.4% for p16-/HPV-, 53.2% for p16-/HPV+, and 54.7%for p16+/HPV- cases (Table 2) (151, 159). Although these two groups (some will "argue" four) have distinct etiologies, the treatment is the same depending on the cancer stage. It includes (surgery, radiotherapy, radiotherapy and chemotherapy, radiotherapy and cetuximab +/- induction chemotherapy, radiotherapy and cisplatin +/- induction chemotherapy), and in recurrent, unresectable, or metastatic disease chemotherapy, immune checkpoint inhibitors, cetuximab, trastuzumab deruxtecan for HER2+ (score 3+) as a tumor-agnostic approach (3, 105, 160-169).

However, it could be an option to personalize treatment for specific patient groups, especially those who are eligible for oropharyngeal HPV-associated de-escalation, but there are still various obstacles and unanswered questions, although cisplatin-based chemoradiotherapy remains the standard of care for locoregionally advanced oropharyngeal cancer (170, 171). Besides HPV-positive oropharyngeal tumors, tumor-infiltrating lymphocytes (TILs) can play an important role in de-escalation treatment strategies. HPV-positive oropharyngeal cancer patients with high TILs exhibited a significantly better overall survival rate compared to those with low TILs (172-174). However, further research is needed to understand the total impact on survival and tailor treatment. Efficient strategies to tackle HPV-positive oropharyngeal cancer are still the subject of many trials and treatment de-escalation can take numerous forms: should we substitute cisplatin for a potentially less toxic agent, for example, cetuximab, although cetuximab showed underpowered regarding cisplatin in overall survival; should we use concomitant chemoradiotherapy with or without induction chemotherapy; should we use a single modality (surgery or radiotherapy) and eliminate chemotherapy; or at least reduce the dose of cisplatin; and lastly which dose of radiotherapy is appropriate without compromising local and distant control and overall survival (159, 175-178)?

Phase 2 clinical studies are ongoing to assess the efficacy and safety of the anti-HPV vaccine in combination with immune checkpoint inhibitors. TheOpcemISA phase 2 study examines the efficacy of the combination of ISA101b (a peltopepimut-S vaccine targeting E6/E7 HPV oncoprotein) with cemiplimab compared to cemiplimab alone in recurrent or metastatic HPV-16-positive oropharyngeal cancer. 198 patients with recurrent or metastatic squamous cell HPV-positive cancer of the oropharynx were included. There was no difference in the overall response rate between the two groups. However, in the sub-analysis, patients who had CPS ≥20 and added ISA101b to cemiplimab significantly increased ORR (28.1% vs. 23.3%) and OS (11.9 vs. 30.1 months) without a significant increase in toxicity (179). On a similar track, other studies were also ongoing, including NCT03978689 with CUE-101 (the first vaccine using the Immuno-STAT platform) in combination with pembrolizumab and NCT04180215 with HB-200 (the arenavirus vaccine) in combination with pembrolizumab in recurrent or metastatic HPV-16-positive head and neck cancers (180-182).

Cervical Screening

Importance of Cervical Screening in Preventing Cervical Cancer

The WHO has recently launched a global initiative aimed at advancing preventive strategies, screening, and treatment for cervical cancer. This initiative prioritizes the expansion of HPV vaccination programs, enhancement of screening and management protocols for both pre-invasive and invasive cervical lesions, and the provision of optimal therapeutic care for women diagnosed with invasive cervical cancer (183). The main goal of cervical screening is the prevention of cervical cancer by detection and treatment of precancerous intraepithelial lesions and early invasive cancers, to decrease mortality rates. There are two types of screenings: (i) organized population-based screening and (ii) opportunistic non-population-based screening. An organized population-based screening program is defined as a program that involves a defined target population, including specific age categories, methods, and intervals of screening. Also, there are mechanisms to identify the eligible individuals and send personal invitations to attend the screening (184). On the contrary, in opportunistic screening, the exams are performed randomly by a healthcare professional, the target population is not systematically invited, and the screening coverage depends on the frequency of visits to a doctor. Numerous studies in the past showed that organized population-based screening programs are more efficient, more cost-effective, and more equally distributed than opportunistic screening (185, 186). They also provide enhanced protection against the negative consequences that can arise from low-quality screenings or screenings conducted too frequently (187).

Overview of Cervical Screening Methods

Currently, the screening tests used in ongoing programs worldwide include cervical cytology, known as Pap test, HPV testing alone, or a combination of HPV testing and cytology. The technique of cervical cytology was developed by Papanicolaou and Babes in the 1920s and later improved by Papanicolaou (188). The conventional cytology technique involves collecting exfoliated cells from the transformation zone and endocervical canal. Cells collected for microscopic examination are applied to a glass slide for conventional cytology and commonly fixed using 95% ethyl alcohol covering the whole cellular area of the slide. According to general recommendations, cytological examinations are best scheduled approximately two weeks after the start of the previous menstrual period. To ensure accurate results, it is important to avoid sexual intercourse within 24 hours before the exam and refrain from using intravaginal estrogen products. Additionally, after childbirth, obtaining sufficient cervical samples for accurate interpretation is challenging until at least 8 weeks postpartum (184, 189). In the 1960s, cervical cytology was implemented for cervical cancer screening in several high-income countries. Over time, the focus of the Pap test has evolved from detecting invasive cancer to identifying precancerous lesions. After the implementation of cervical screening, there was a substantial decrease in the incidence of cervical cancer. It has been shown that in countries with a well-organized cytological screening, performed every three to five years in the age range from 35–64 years, the incidence of cervical cancer is reduced by 80% or more among screened women (190). It has been well-established that persistent infection with specific HPV types is closely linked to the development of cervical precancerous lesions and cancer. This understanding has prompted the consideration of detecting HPV genetic sequences as a potential alternative to traditional screening methods that rely on the microscopic examination of cervical cells (184). For the past two decades, HPV testing has emerged as a pivotal tool in cervical cancer prevention, offering a more precise approach to detecting high-risk HPV types associated with cervical malignancies. Today, there is an abundance of commercially available HPV tests. Most of these tests target multiple alpha-papillomaviruses types, including those with significant clinical relevance due to their carcinogenic potential. Specifically, 12

types, known as the IARC-2009 high-risk HPV types, are classified as carcinogenic (Group 1) by the IARC. These include HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 (191). HPV-based screening offers 60-70% greater efficacy in protecting against invasive cervical cancer compared to cytology. Evidence from extensive randomized trials supports the initiation of HPV-based screening starting at age 30 and recommends extending screening intervals to a minimum of 5 years (192). Many trials compared co-testing (HVP and cytology) to HPV primary testing alone. Evidence suggests that co-testing is associated with higher costs, increased referral rates to colposcopy, and reduced positive predictive value for CIN2+ detection among referred women (193, 194).

Therefore, according to the WHO strategy for the elimination of cervical cancer, it is recommended that the screening should be performed with a high-performance test equivalent to or better than the HPV test (183). Over the past decade, numerous studies have examined the efficacy of collecting cervical material for HPV testing via vaginal self-sampling, to increase participation in cervical screening programs, particularly among women who are less likely to attend screening. The sensitivity of HPV testing for identifying cervical precancerous lesions and cancer using self-collected cervicovaginal samples was proved to be equivalent to that observed with conventional cytology or liquid-based cytology conducted with clinician-collected samples. However, the specificity of HPV testing with self-collected samples tends to be lower (195). With the development of more precise diagnostic tests, the use of self-collected samples for HPV testing could be considered a viable alternative in organized, population-based screening programs, particularly for women who have not participated in screening despite receiving a personal invitation (196). Aside from Pap and HPV tests, there is another affordable and straightforward technique, known as visual inspection with acetic acid (VIA). This screening method is widely utilized in mass screening programs in low-income regions. By applying a 3-5% acetic acid solution to the cervix, nuclear-dense lesions become visible as acetowhite areas. This test has a specificity of 82% (ranging from 64-98%) and a sensitivity of 84% (ranging from 66-96%), although it has a high rate of false positives (197).

Current Status and Challenges of Cervical Screening in BH

Although BH adopted screening protocols in alignment with recommendations from international health organizations, the implementation has progressed very slowly. According to the "Strategy for Prevention, treatment and Control of malignant diseases 2012-2020", in 2011 the government of the FBiH set a goal to implement and improve the organized population screening for cervical cancer, by developing individual population screening programs according to expert's consensus criteria and European recommendations on age and frequency, including the screening for cervical cancer for women based on cytological examination (198). To date, the screening program has been conducted on an opportunistic basis and includes mostly cytological examination and, in some parts of the country, HPV testing (199).

Comparisons with Cervical Screening Programs in Other Countries

More data regarding the screening program for cervical cancer are available from neighboring countries. In Serbia, there was notable progress in advancing preventive healthcare services for women's reproductive health, by initiating organized cervical cancer screening in 2012. To date, four screening cycles, each spanning three years, have been conducted among women aged 25 to 64. The current cervical cancer screening coverage across Serbia ranges from 35% to 68%, with evident regional disparities (200). According to the Institute for Public Health of Croatia, the Government adopted the National Program for Early Detection of Cervical Cancer in 2010, with its implementation commencing in December 2012 (201). During the initial implementation cycle (2013-2016), of the 414,018 women invited for screening, only 10%

responded to the test invitation. According to the European Health Interview Survey in 2019, the results of the second screening cycle in Croatia showed that a significant proportion of women aged 20-64 (76%) underwent a Pap test in the previous three years, while only 5% reported never having had the test (202).

In Montenegro, an organized and centralized cervical cancer screening program was initially launched as a pilot project in July 2016. Since February 2018, this program has been implemented nationally, targeting women aged 30 to 50 years. The primary screening method employed is HPV genotyping, with a screening cycle scheduled every five years (203). A review published in 2022 reported that the screening coverage in BH over five years was 30%, which is lower compared to neighboring upper-middle-income countries. Specifically, Serbia, North Macedonia, and Albania reported coverage rates of 66%, 67%, and 58%, respectively. In Montenegro, the coverage rate was 39%. For comparison, the average coverage of five-year screening programs in high-income countries is 77%, with coverage rates ranging from 66% to 88% (204).

HPV Vaccination

Overview of HPV Vaccines (Types, Efficacy, and Recommendations)

Persistent infection with high-risk human papillomavirus (HPV) types is the leading cause of cervical cancer, and HPV vaccines are a critical tool in preventing this and other HPV-related cancers. To effectively combat these HPV-related cancers, significant efforts are required to develop and implement efficient vaccination programs and strategies (205). Three main HPV vaccines that have been licensed and widely used are Cervarix, Gardasil, and Gardasil 9. Cervarix (GSK, Rixensart, Belgium) is a bivalent vaccine that targets HPV-16 and 18, which cause about 70% of cervical cancer cases. It is particularly effective in preventing cervical cancer but does not cover types that cause genital warts. Next, in line is Gardasil (Merck & Co, Whitehouse Station, NJ, USA), a quadrivalent vaccine with broader protection, covering HPV-6, 11, 16, and 18. Application has been widespread for both cervical cancer as well as genital warts. The most comprehensive option is Gardasil 9 (Merck &Co, Whitehouse Station, NJ, USA), a nine-valent vaccine showing protection against nine HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. This vaccine offers expanded protection by targeting additional HPV strains, covering approximately 90% of cervical cancer cases and most genital warts. As a result, it is often the preferred choice in various vaccination programs due to its comprehensive coverage (206). All three HPV vaccines—Cervarix, Gardasil, and Gardasil 9—are developed using virus-like particles (VLPs), which are made from the L1 protein of the human papillomavirus (HPV). These L1 proteins self-assemble into VLPs that mimic the structure of the actual virus, but without containing any viral DNA. As a result, VLPs are non-infectious and cannot cause disease, making them a safe and effective foundation for vaccines. The resemblance of these VLPs to the natural virus plays a crucial role in their effectiveness. When introduced into the body, they trigger a strong immune response, allowing the immune system to recognize and produce antibodies against HPV. This response equips the immune system to quickly identify and neutralize the virus if the individual is exposed to it in the future. The high immunogenicity of the VLPs ensures that even without the use of strong adjuvants, the vaccines provide long-lasting protection against the targeted HPV types.

Clinical trials and long-term studies have shown that these vaccines have been effective in preventing infection for many years, significantly reducing the risk of HPV-related cancers and conditions. Moreover, because VLPs closely mimic the virus's outer shell, they generate an immune response that is both robust and specific to the HPV types they represent. This mechanism helps establish a strong memory response in the immune system, providing durable protection and reducing the incidence of HPV-related diseases in vaccinated populations (207). The current HPV vaccine

recommendations by the Advisory Committee on Immunization Practices (ACIP) recommend routine HPV vaccination for all preteens aged 11-12 years, though it can be started as early as age 9. The WHO endorses HPV vaccination for girls starting at age 9. For those who receive their first dose before the age of 15, a two-dose schedule is recommended, with the second dose given six to 12 months after the first. For those vaccinated after age 15 or those with certain immunocompromising conditions, a three-dose schedule is advised. Additionally, ACIP extended recommendations to include catch-up vaccination for everyone through age 26. Additionally, individuals aged 27-45 who were not adequately vaccinated earlier and are at risk of new HPV infections may also benefit from vaccination, though this is typically decided on a case-by-case basis with healthcare providers (208). When it comes to safety, HPV vaccines are well-studied and considered safe. Common side effects include mild pain, swelling, or redness at the injection site.

A systematic review by the WHO found no significant difference in serious adverse events between those vaccinated and those who received a placebo. The risk of severe reactions, such as anaphylaxis, is very low, estimated at 0.3-3 cases per million doses administered. Furthermore, extensive data analysis has shown no causal link between the vaccine and conditions like Guillain-Barré syndrome, complex regional pain syndrome (CRPS), or primary ovarian failure. WHO advises against the use of the HPV vaccine during pregnancy as a precautionary measure. However, research indicates that inadvertent administration of the vaccine during pregnancy does not elevate the risk of adverse outcomes for either the mother or the infant (208, 209). The results of the meta-analysis have confirmed that HPV vaccines do not result in increased risks of obstetric or birth complications (210).

Status of HPV Vaccination Programs in BH

BH is at the bottom of the ranking (immediately after Azerbaijan) in its HPV prevention efforts. BH faces challenges due to the absence of robust primary and secondary prevention strategies, including comprehensive vaccination programs and HPV screening services. Furthermore, it lacks reliable, evidence-based information on HPV prevention, which impedes public awareness and access to necessary preventive measures (211). What adds to the complexity of the issue is that healthcare responsibilities are divided among the FBiH, Republika Srpska (RS), and Brčko District (BD), each managing their healthcare initiatives, including HPV vaccination programs. As of mid-2021, FBiH had not integrated HPV vaccination into its health plans, and no vaccination programs were in place.

However, progress had been made in Canton Sarajevo where a free, voluntary HPV vaccination program for girls aged 11-12 using the 4-valent Gardasil vaccine began in November 2022, and by December 2023, the program was extended to include females aged 11-26. Additionally, pilot programs for girls aged 13-14 started in January 2023 in three other cantons, with plans to expand to the remaining six cantons by September 2023. In Republika Srpska, while HPV vaccination was recognized in health policies by mid-2021, no programs had been implemented. By June 2023, HPV vaccination was added to the Immunization Calendar, offering free, voluntary shots for girls and boys aged 11-14 through primary health clinics using the 9-valent Gardasil vaccine. The vaccine is also available for those aged 15 and older through regional public health units, although it's not free. Details on HPV vaccination in Brčko District were not provided, suggesting that further information might be needed to understand the status there (15). Given the estimated effectiveness of the current HPV vaccines, which could prevent up to 77.8% of cervical cancer cases in BH associated with HPV-16 and 18, there is significant potential for reducing the incidence of this disease. Additionally, if the cross-protection offered by these vaccines against non-vaccine HPV types proves to be long-lasting, an additional 6-10% of cases could be prevented (11).

Comparison with HPV Vaccination Coverage in Other Countries

Leading countries in HPV prevention include Denmark, Sweden, Finland, the United Kingdom, and Ireland. These nations have set a high standard by implementing comprehensive, best-practice policies. Their approach features gender-neutral vaccination programs that are freely available to all eligible individuals, resulting in notably high vaccination coverage. Additionally, they offer free HPV screening for adults, ensuring early detection and prevention of HPV-related conditions. These countries also excel in providing accessible and reliable information through government-supported websites, which help educate the public about HPV and its prevention (211). Coverage was highest in Australia, New Zealand (77%), and Latin America (61%), while Europe and North America reached 35%. In contrast, Northern Africa, Oceania (excluding Australia and New Zealand), and Asia had low coverage rates. Despite limited introduction in sub-Saharan Africa, nearly 20% coverage was achieved due to effective programs (212).

Barriers to Vaccine Access and Availability

As of June 2020, 107 out of 194 WHO Member States (55%) have introduced HPV vaccination nationwide or partially. However, the distribution is uneven: 85% of countries in the Americas and 77% in Europe have introduced the vaccine, compared to only 41% of low- and middle-income countries (LMICs) by the end of 2019. In 2019, 87% of new introductions occurred in LMICs, with six countries in sub-Saharan Africa, five in Latin America and the Caribbean, and three in Asia and the Pacific joining the program. GAVI has supported 19 LMICs, representing 35% of these countries. Thirty-three out of 107 programs (31%) were "gender neutral," vaccinating both boys and girls. Most programs (47%) targeted 12-year-olds, but LMICs generally targeted younger girls (9-10 years). In 2019, at least 35 million girls aged 9-14 were targeted, with 25 million in LMICs and 10 million in high-income countries (HICs). School-based delivery was the primary method in LMICs (90%), while HICs used both school-based (39%) and facility-based (48%) approaches. Globally, only 15% of girls and 4% of boys completed the full HPV vaccination course by 2019, with 20% and 5% receiving at least one dose, respectively, as shown in Figure 2 (212, 213). Seven of the ten most populous countries, including China, India, and Nigeria, have not fully introduced HPV vaccination, which affects global coverage, limiting it to 15%. Among the girls living in countries with HPV programs, only 53% received the final dose. Program performance averaged 67% for the first dose and 53% for the final dose. LMICs had higher first-dose coverage (80% vs. 72% in HICs) but also higher dropout rates (18% vs. 11%). Only five countries (6%) achieved over 90% coverage for the final dose, the target for global cervical cancer elimination by 2030. Twenty-two countries (21%) exceeded 75% coverage, while 35 countries (40%) had 50% or lower coverage, with 14 countries (16%) below 20%. By comparison, only 3% of countries globally have DTP3 vaccine coverage below 50% (212).

Public Health Implications and Recommendations

Impact of Inadequate Screening and Vaccination on Public Health

High-risk HPVs spread through sexual contact and are linked to anogenital and oropharyngeal malignancies (214, 215). On May 19, 2018, the Director General of WHO issued a global call to action aimed at eliminating cervical cancer, which has the greatest HPV-related disease burden (>90%). The main strategies that all countries should achieve by 2030 include 90% of girls fully vaccinated with the HPV vaccine by age 15, 70% of women screened with a high-performance HPV test by age 35 and again by age 45, and 90% of women with the cervical disease treated (15).

According to the Federal Ministry of Health's 2020 public health report, the second most common cause of death in the FBiH in 2020 was

malignant neoplasms (C00-C97). Women had a considerably greater incidence of cancer than men in the age range of 25 to 54 (54). Cervical cancer is the second most frequent female cancer in BH, as well as the third major cause of cancer death in women aged 15 to 44 years (76). Although the 2020 report does not include information on the prevalence of HPV infections and HPV-related malignancies, we could anticipate that this incidence may be linked to the fact that, besides breast cancer, HPV-related cancers such as cervical cancer are more common in this age group. Because of inadequate and ineffective screening, several countries in Central and Eastern Europe have a high cervical cancer burden; the estimated 14,300 new cases and 7200 deaths in 2008 are expected to rise 5% and 15%, respectively, to 15,000 cases and 8300 deaths by 2030 (28). The prevalence of HPV infections in women with normal cervical cytology in Central and Eastern Europe (based on samples from Croatia, the Czech Republic, Hungary, Lithuania, Poland, and Slovenia) revealed an overall prevalence of infection with high-risk HPV types of ~11% (28). However, reports from BH indicate a significantly greater prevalence. In a 10-year cross-sectional study of a Bosnian cohort of 1517 routinely screened women, 653 (43%) tested positive for HPV. Out of all the HPV-positive patients, 386 (59%) were infected with only one type of virus. HPV-16 was the most prevalent type (22.5%); however, the majority of patients were infected with HPV-16 or HPV-18 in combination with other HPVs. The average age of HPV-positive patients was 33.38±7.85, with a range from 18 to 61 years (Table 1) (18). In another study of women with positive cervical cytology (N=105), 16 different HPV strains were identified, with the majority being high-risk HPV types. HPV-16 was the most commonly found genotype in ~33% of women, while HPV-18 was detected in 7.5% of women (Table 1) (24). A report from nine Central and Eastern European countries (Bulgaria, Croatia, the Czech Republic, Hungary, Poland, Romania, Serbia, Slovakia, and Slovenia) provided quantitative evidence on the impact of early death due to HPV-related cancers in 2019. The societal and economic impact was calculated by analyzing the *"productivity loss of early death owing to HPV-related cancer, years of life lost (YLL), years of productive life lost (YPLL), and the present value of future lost productivity (PVFLP)"*. In 2019, HPV-related cancers caused 6,832 deaths, 107,846 YLL, 28,330 YPLL, and a PVFLP of approximately €151 million. Cervical cancer had the highest mortality burden, accounting for 72% of deaths, as well as the biggest PVFLP, at €114 million, accounting for 76% of total PVFLP (215). Although this report does not include data from Bosnia and Herzegovina, it demonstrates the socioeconomic burden of HPV-related malignancies, which result in significant productivity losses. If we consider that the life expectancy at birth for the FBiH population in 2019 was 77.13 years, slightly higher for women (79.25) than for men (74.93) according to the 2020 report, we can only anticipate negative effects of HPV-related carcinomas on socioeconomic aspects, regardless of the high unemployment rate (54). The prospective benefit of high-coverage HPV vaccination is expected to help reduce this increasing burden. For example, in the United States, the percentage of preventable cancers based on HPV-positive cancers would be nearly 80% through uptake of the 16/18 vaccine, with an additional 13% of cancers avoidable through the 9-valent vaccine, indicating a more than 90% decrease in HPV-positive cancers (2). In Europe, the total number of cancer cases that could be avoided by vaccinating girls and boys at present vaccine uptake ranged from 318 and 168 per cohort of 200,000 preadolescents (100,000 girls plus 100,000 boys) in Croatia (<20% uptake of the 9-valent vaccine) to 1904 and 467 in Estonia (<70% uptake of the 9-valent vaccine) (214). Many reports assessed the cost-effectiveness of HPV vaccination programs.

The WHO suggests that cost-effectiveness should be considered before introducing the vaccine, particularly in countries with limited resources. For national decision-making, the PRIME (Papillomavirus Rapid Interface for Modeling and Economics) model can be used to assist country-led data gathering and provide more individualized outcomes (216, 217). A report from Central

and Eastern Europe and Central Asia (CEECA) on the cost-effectiveness of the HPV-16/18 vaccine for 12-year-old girls found that the HPV-16/18 vaccination was very cost-effective in 25 of 28 countries, including Bosnia and Herzegovina (218).

Strategies to Improve HPV SCREENING and Vaccination Rates in BH

Despite marked technological improvements worldwide, BH still faces huge challenges in enhancing public health because of complex political and healthcare systems and the lack of a national cancer registry 30 years after the war. The primary goal of the cancer registry is to obtain, code, and categorize all malignancies to generate statistics on the occurrence of cancer in certain populations during a specific period and provide a system for monitoring and controlling the impact of cancer on the community. Cancer incidence statistics generated by registries can be used in a wide range of cancer control areas, including etiological research, early detection, assessment of outcomes, and overall healthcare planning (219). From all the above, we cannot even conclude which category we fall into: "the good, the bad, or the ugly."

The main strategies for reducing the prevalence of HPV infections and HPV-related malignancies should be the implementation of the HPV vaccine, adequate screening of target populations, and improvement of treatment through the introduction of new therapeutic options and the expansion of existing indications through the Federal Institute of Health Insurance. Prevention strategies are the gold standard for reducing the risk and prevalence of diseases. Therefore, it is crucial to prioritize evidence-based awareness campaigns promoting HPV vaccination to enhance cancer prevention and combat misinformation, ultimately increasing health literacy. For HPV prevention purposes, additional efforts could be made through educational workshops in schools and educational institutions, by introducing or strengthening the system of inviting and reminding about vaccination, consultations organized through youth associations or associations of cancer patients, and also STD counseling centers for the youth and persons with high-risk sexual behavior and the LGBT population. For the prevention of HPV-related malignancies, the implementation of the National Cervical Cancer Early Detection Program will provide access to cervical cancer screening, diagnostic, and treatment services. In addition to the political will to accelerate the introduction of HPV prevention programs, there is a need to build infrastructure, including high-quality cytological testing.

Role of Healthcare Policy and Education in Cancer Prevention

According to the Health Care Law, primary healthcare involves strategies that preserve and enhance the population's health, such as disease and injury prevention, treatment, and rehabilitation; identification and management of risk factors for noncommunicable diseases; youth preventive health care; immunization against infectious illnesses; rehabilitation and medical treatment; palliative care; and so on (54). All these facts suggest that healthcare providers play a valuable role and have legal liability in healthcare education among the general population as well as in high-risk groups. Doubts regarding the security and efficacy of vaccines are seen to be increasing among the public.

According to the World Health Organization, vaccine hesitancy is defined as a delay in accepting or refusing immunization regardless of the availability of vaccination services (220). Healthcare workers (HCWs) are trusted providers of medical information, yet their skepticism about vaccinations may impact vaccine coverage. A study of Croatian HCWs primarily employed in epidemiology and public health, school medicine, pediatrics, and general practice/family medicine found that 17% of primary HCWs were vaccine-hesitant, with a significant distinction between physicians and nurses (7% vs. 24.9%) (221). This finding is concerning because nurses tend to spend more time with patients, engaging in less formal interactions, and providing guidance and assistance daily. According to the 2020 Public Health Report and

2018–2019 BiH Youth Study, only 13% of young people in BiH have a university degree, 50% have a three-year secondary education, and 4% have no formal education. Data on computer literacy was collected from 1,229,972 respondents, with 38.7% declaring themselves computer illiterate (54). To ensure successful prevention, healthcare workers must have greater knowledge of and offer additional information about measures like HPV vaccines. Because vaccine hesitancy in HCWs can have a significant impact on the national vaccination program's implementation, it is critical to increase confidence among primary HCWs and address vaccination-related knowledge gaps, particularly in the nursing population, through systematic vaccination training for healthcare workers.

Future Directions

Potential Areas for Research and Policy Development

The substantial global burden of HPV-related cancers underscores the urgent need for comprehensive research in this area and effective prevention strategies. While progress has been made, significant challenges persist, particularly in countries like BH. Europe Beating Cancer Plan has initiated a comprehensive effort to eradicate HPV-related cancers through increased HPV awareness, widespread vaccine availability, and effective cervical cancer screening (222). Key goals are to achieve HPV vaccination rates of 90% for girls and to significantly increase the vaccination of boys by 2030 in Europe. These European initiatives offer valuable guidance for BH. Addressing fundamental challenges, such as establishing a functional comprehensive cancer registry, is a prerequisite for effective HPV prevention and control strategies in BH. To effectively implement and evaluate HPV prevention strategies, a central HPV vaccination registry is essential, given the current absence of comprehensive HPV prevalence data in BH. Data from the literature suggests that high vaccine costs and negative public perception have been primary obstacles to the widespread adoption of HPV vaccination programs in Central and Eastern European countries (27).

To address these challenges in BH, targeted public awareness campaigns are crucial. Similar to the prevention of other infections (e.g., COVID-19), public awareness campaigns about HPV infection, its consequences, and the importance of prevention are vital to promoting public support for HPV vaccination. These should emphasize the advantages of vaccination while proactively addressing misinformation (64). Implementing fully reimbursed vaccination programs and integrating HPV screening into national cancer plans are essential steps toward improving vaccination rates and cervical cancer prevention in BH.

Importance of Continued Surveillance and Data Collection

Continuous surveillance and robust data collection are needed for the successful implementation and evaluation of HPV prevention strategies. A comprehensive national immunization register is essential for monitoring vaccination coverage, identifying disparities, and evaluating the impact of interventions. By creating a comprehensive national HPV register it would be possible to track progress, identify challenges, and measure the impact of the interventions. For example, by identifying specific challenges such as low vaccination rates, vaccine hesitancy, or access barriers, targeted interventions can be implemented to enhance HPV prevention efforts. This approach facilitates data-driven decision-making to optimize resource allocation, target high-risk populations, and refine prevention strategies. Knowledge and experience sharing with regional and European countries can significantly enhance the effectiveness of HPV infection prevention strategies in BH. The high prevalence of high-risk HPV types 16 and 18 among younger women in BH underscores the need for a screening program prioritizing these specific subtypes. The identification of HPV in nearly half of oral and head and neck cancer cases in BH underscores the broader impact of HPV infection beyond cervical cancer (13). Eliminating

structural barriers and expanding vaccination access are important to achieving optimal HPV prevention outcomes.

Conclusions

Studies conducted in BH revealed a high HPV prevalence among women. HPV-16 has consistently been identified as the most common subtype in women with normal cervical cytology, preinvasive cervical changes, and cervical cancer. Furthermore, literature research has revealed a high HPV prevalence in HNC and colorectal cancers. HPV-related cancers have a significant public health burden, particularly in less developed countries like BH where access to prevention and screening services is limited. Despite the well-established link between HPV and cervical cancer, as well as other malignancies, a comprehensive literature search reveals that no HPV prevention or screening program has been implemented in BH. Key challenges to progress include the absence of a unified cervical cancer screening program, limited HPV vaccination coverage, and the lack of comprehensive cancer and HPV registry data. However, recent efforts to incorporate HPV prevention into national health strategies represent a positive step forward.

Final Thoughts on Improving HPV-Related Cancer Outcomes in BH

Our review offers a comprehensive overview of existing studies in BH, providing valuable insights into HPV genotypes that can guide the development of effective prevention strategies. To effectively reduce the burden of HPV-related cancers in BH, a comprehensive approach is essential. This includes prioritizing the implementation of a national HPV vaccination program and establishing a cervical cancer screening program. Additionally, investing in research and raising public awareness are required components of a successful HPV prevention strategy. By addressing these challenges and implementing evidence-based interventions, BH can significantly improve cancer outcomes and reduce the impact of HPV-related diseases on public health. Further research is necessary to explore the complete extent of HPV-related cancer in BH and to inform the development of targeted prevention strategies.

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