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Research Article

Impact of risk and protective factors for Human papillomavirus infection and the associated diseases among adult women

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Summary

The main risk factors for Human papillomavirus (HPV) infection, and the development of associated diseases are related to sexual behavior and health literacy of the population. The study aimed to investigate the impact of risk and protective factors for HPV infection and the development of associated diseases in adult women. A case-control study was conducted from January 2020 to May 2022A. Respondents had sought outpatient and/or inpatient obstetric-gynecological care in the city of Pleven. The significance of results, findings, and conclusions was determined at $p < 0.05$, and the odds ratio (OR) was calculated. Data analysis identified three out of the 15 factors as significant: lower education (primary and secondary) OR = 2.36 95% CI (0.97–5.74), lack of vaccination against HPV OR = 2.05, 95% CI (0.86–4.92), and urban residence OR of 1.29 95% CI (1.11–1.52). Two factors with a protective effect on HPV infection were statistically significant: education (secondary and higher) ($p = 0.05$) and rural residence ($p = 0.001$). Improving health literacy among the population and enhancing preventive measures related to HPV and its associated diseases would reduce the impact of risk factors.

Key words: Health literacy, HPV, risk factors

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Introduction

Human papillomavirus (HPV) is responsible for the most common sexually transmitted infections globally. Various literary sources predict that over 80% of sexually active women and men will become infected with the virus at least once (Kombe et al. 2021).

The main risk factors for HPV infection and the development of associated diseases are related to sexual behavior and the health literacy of the population. Various literary sources categorize risk factors into several major groups:

1. Risk factors related to lifestyle
1.1. Low health literacy

In 2016, Rashid and colleagues conducted a study among students in India regarding their awareness and knowledge about HPV, HPV vaccines, and cervical

cancer. Data analysis revealed that students studying advanced biology had better health literacy than those who did not. The authors reported that 46.58% of biology students indicated knowledge about HPV, and 43.62% were informed about the vaccine against the virus. For students not studying biology, the data were as follows: 21.93% were familiar with the virus and its connection to cervical cancer, and 28.06% were informed about the vaccine. The authors concluded that the awareness of the participants about HPV, its vaccines, and cervical cancer is insufficient (Rashid et al. 2016).

In 2019, Kasymova and colleagues conducted a study among 256 students in South Carolina. The authors found that respondents had serious gaps in their knowledge about prevention, symptoms, and complications related to HPV. They reported that HPV remains a significant problem in the USA. In conclusion, Kasymova et al. emphasized the need for additional education regarding HPV (Kasymova et al. 2019).

In 2019, Belotserkovtseva and colleagues conducted a study among 389 high school students in Russia. The study data showed that only 23.5% of the respondents regularly used barrier methods to protect against sexually transmitted diseases. The study demonstrated low health literacy among adolescents aged 14–17 (Dmitrievna Belotserkovtseva and Igorevna Mayer 2020).

In 2021, Wang and colleagues conducted a study about the awareness and knowledge related to HPV infection among students in a vocational medical school in China. The authorship concluded that the awareness and knowledge of the respondents were insufficient. The study identified female students as more informed about cervical cancer, with an odds ratio OR = 1,84, 95% CI (1,43, 2,35). The authors emphasized that increasing awareness is linked to age and the level of education at school ($p < 0.05$) (Wang et al. 2021).

Yacouti et al. (2022) investigated the awareness of 1087 female students from six universities in Morocco regarding HPV. The authors found that only 14.7% of the respondents knew about HPV infection, and only 7.8% were informed about the HPV vaccine. Analyzing the data, the authors concluded that changing the levels of health literacy related to HPV and its vaccines requires the development of various educational programs, including the prevention of cervical cancer (Yacouti et al. 2022).

1.2. Smoking

WHO identifies cigarette smoking as a risk factor for persistent HPV infection. Smoking reduces immunity, including local immunity, hindering the body's ability to fight the virus. Therefore, smokers have a high risk of developing oropharyngeal cancer. In 2021, Utami and colleagues published a seven-year study, concluding that the proportion of individuals infected with high-risk HPV types is higher among tobacco users than non-users (Utami et al. 2021).

1.3. Weakened Immunity

Weakened immunity accelerates the development of complications associated with HPV and the body's inability to cope with the infection. Frequent illness is also a risk factor. A decrease in immunity is a prerequisite for the body's

inability to fight HPV and to achieve "self-cleaning." On the contrary, the infection may develop rapidly or persist. Weak immunity leads to the reactivation of viral infection (Hewavisenti et al. 2023).

2. Risk factors related to obstetric-gynecological status

2.1. Early onset of sexual activity

The age group of 10–16 years is defined as an early age for the onset of sexual activity. The authors identify this age as a precursor for early encounters with HPV. The explanation is that the tissue covering the vagina and cervix is still immature and easily vulnerable, making it an easy entry point for viral cells (Dmitrievna Belotserkovtseva and Igorevna Mayer 2020).

Itarat et al. (2019) conclude that early sexual contact increases the risk of infection with the oncogenic strain of HPV-16. The authorship calculates that an age below 19 for the onset of sexual activity increases the risk of HPV infection by 1.53 times (OR = 1.53, 95% CI 0.90–2.61) (Itarat et al. 2019).

2.2. Multiple sexual partners

An increase in sexual partners leads to an increased risk of virus infection. The number of sexual partners is not considered a primary risk factor for encountering HPV, but having multiple sexual partners increases the risk of HPV type 18 infection (OR = 4.58; 95% CI 1.44–14.58) (Itarat et al. 2019).

Multiple sexual partners are considered a potential risk factor, as noted by Liu ZC et al. (2015), who calculate that the risk of developing invasive cervical cancer is 1.77 times higher in exposed individuals (OR = 1.77, 95% CI 1.50–2.05) (Liu et al. 2015).

2.3. Past sexually transmitted infections

Sexually transmitted infections are considered a risk factor. The disruption of the epithelial layer of the genital area is an entry point for viral DNA and the development of infection (Kostova 2012). Literary sources consider the likelihood of developing cervical dysplasia in patients who have experienced sexually transmitted infections. In 2020, Dmitrievna et al. found the presence of Chlamydia infection (9.09%), Ureaplasma (27.27%), and Mycoplasma infection (9.09%) in HPV-positive women. The authors note that Chlamydia infection is determined to be a co-factor in the development of cervical dysplasia (Dmitrievna Belotserkovtseva and Igorevna Mayer 2020).

2.4. First birth at age under 20

The underdeveloped female body can easily be subject to viral infection. Additionally, different tears during childbirth provide an easy route for the entry of viral particles and the subsequent development of HPV-associated disease.

In 2020, Lintao and colleagues described early age for first pregnancy and childbirth as a risk factor. The authors calculated that the risk of developing cervical cancer for those who had their first sexual contact and first pregnancy at or before 16 years is 2.36 times higher (OR = 2.36; 95% CI 1.82–3.07). The

risk for women who made their sexual debut and became pregnant at 17–20 years old is 1.93 (OR = 1.93; 95% CI 1.58–2.36) (Lintao et al. 2022).

According to data from the National Statistical Institute (NSI) in Bulgaria, during 2010–2022, the live births of women under 20 were 85,616(Anastasiou et al. 2022). The distribution by years is shown in Table 1.

Table 1. Number of live births in Bulgaria from women under the age of 20 during the period 2010–2022.

Year	Number of live births	%
2010	8 411	11.1%
2011	7 799	11.0%
2012	7 404	10.7%
2013	6 968	10.5%
2014	6 655	9.8%
2015	6 274	9.5%
2016	6 031	9.3%
2017	6 038	9.4%
2018	6 191	10.0%
2019	6 245	10.1%
2020	5 970	10.1%
2021	5 861	10.0%
2022	5 769	10.2%

The data shows that the number of live births from women under the age of 20 is decreasing, reaching 5,769 in the year 2022, corresponding to 10.2% of all live births in the same year. Analyzing the data reveals that as the overall number of live births decreases, the number of births from mothers under 20 also decreases. Over the past 12 years, the percentage ratio of these two indicators has varied between 9% and 11% (National Statistical Institute).

2.5. Use of oral contraceptives (OC)

Literary sources indicate that the use of OCs increases the risk of HPV infection. OCs do not protect against sexually transmitted diseases, and viral infection is considered one of them. While these medications prevent unwanted pregnancies and regulate hormonal balance in women, they do not act as a barrier method for protecting against sexually transmitted diseases and infections (Hinkova et al. 2010).

Anastasiou E. and colleagues (2022) published a systematic review of prospective studies related to the relationship between cervical dysplasia and the use of oral contraceptives. The authors describe seven studies, one of which finds that the use of OCs containing progestin increases the risk of third-degree cervical dysplasia (CIN III) (OR = 1.29, 95% CI 0.48–3.44) (Anastasiou et al. 2022).

The analysis of the literary sources indicates that the risk factors associated with HPV infection and the development of associated diseases are primarily linked to lifestyle and behavior. HPV is a global issue that leads to challenges in all healthcare systems.

Our study investigated the influence of risk and protective factors for HPV infection and the development of associated diseases in adult women.

Materials and methods

An epidemiological case-control study was conducted between January 2020 and May 2022 to identify the risk factors for HPV infection and the development of associated diseases. The study included women who had been patients at the Department of Obstetrics and Gynecology at St. Marina Hospital – Pleven and Hinkomed Medical Center – Pleven.

Cases were defined as women diagnosed with HPV infection or HPV-associated diseases. An appropriate control was unintentionally and randomly selected for each case from women with other gynecological conditions or clinically healthy women who visited the same clinics on the same day.

For the study, an original questionnaire with 47 questions was developed. It included information regarding the demographic and socio-economic status of the women, anamnestic data related to obstetric history (pregnancies, births, abortions), and gynecological status (presence or absence of genital pathology, presence or absence of HPV infection and/or associated diseases), and others.

Statistical data analysis was performed using the software tools MS Office Excel 2019 and SPSS v.28. Significance of results, findings, and conclusions was determined at $p < 0.05$. The odds ratio (OR) was calculated.

Results

The study included 200 participants divided into two groups: 100 patients diagnosed with HPV-associated diseases and control group included 100 clinically healthy women with other gynecological conditions. The respondents were distributed across several age groups, as shown in Fig. 1.

According to the educational level attained by the respondents, they are distributed into four groups, as presented in Fig. 2.

The distribution of participants in the study based on their lifestyle and habits is presented on Table 2.

Through the data analysis, factors that increase the risk of HPV infection and the development of associated diseases were differentiated (Table 3).

Out of the 15 factors examined, three were statistically significant, including primary and secondary education OR = 2.36 95% CI (0.97–5.74), lack of HPV vaccination OR = 2.05 95% CI (0.86–4.92), and urban residence OR = 1.29 95% CI (1.11–1.52).

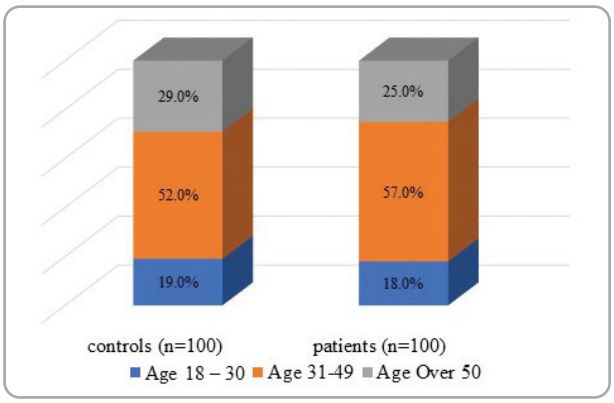

Figure 1. Distribution of Respondents by Age Groups.

Table 2. Characteristics of respondents according to their lifestyle and habits.

Characteristic	Case Group (n = 100)	Control Group (n = 100)
Residence		
City	67.00%	87.00%
Village	33.00%	13.00%
Marital Status		
Married	62.00%	64.00%
Not Married	38.00%	36.00%
Frequency of Gynecological		
Examinations		
Twice a year	15.00%	17.00%
Once a year	42.00%	37.00%
Every 2–3 years	27.00%	27.00%
Only when problems arise	15.00%	19.00%
Childbirth		
Yes	64.00%	74.00%
No	36.00%	26.00%
Abortion*		
Yes	26.00%	36.00%
No	73.00%	62.00%
Smoking		
Yes	45.00%	52.00%
No	55.00%	48.00%
Vaccinated against HPV		
Yes	9.00%	17.00%
No	74.00%	68.00%
Do not know	17.00%	15.00%

*The responses do not sum up to 100% due to the lack of answers of three respondents.

Table 3. Factors Increasing the Risk of HPV Infection and Associated Diseases.

Factor	OR	CI	P
Age 18–30	1.12	0.64–1.95	0.70
Education (Elementary and Secondary)	2.36	0.97–5.74	0.05
Residence – City	1.29	1.11–1.52	0.001
Smoking – Yes	1.16	0.86–1.54	0.32
HPV Vaccination – No	2.05	0.86–4.92	0.11
Gynecological Examinations 2–3 times a year or only when problems arise	1.16	0.66–2.02	0.61
Sexual Contacts – Yes	1.03	0.88–1.20	0.74
Non-use of contraceptives	1.55	0.86–2.79	0.15
Use of hormonal contraceptives. “spiral.” and interrupted intercourse	1.21	0.59–2.45	0.59
Childbirth – Yes	1.16	0.96–1.4	0.12
Vaginal Delivery	1.13	0.85–1.45	0.32
Abortions – Yes	1.39	0.92–2.13	0.11
Gynecological Surgeries – Yes	1.38	0.96–2.03	0.07
Coexisting Gynecological Diseases – Yes	1.42	0.82–2.45	0.20
Family Members with Gynecological Oncological Diseases – Yes	1.04	0.70–1.54	0.84

RR = 27.46 95% CI (13.52–55.79).

In addition to factors that increase the risk of HPV infection and associated diseases, the study also identified protective factors (Table 4).

Based on the analysis of the data, three out of the 15 factors that have a protective effect on HPV infection and associated diseases are statistically significant: education (secondary and higher) (p = 0.05) and rural residence (p = 0.001).

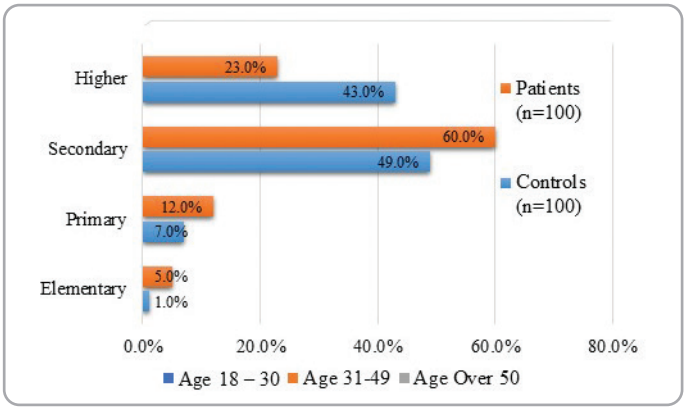

Figure 2. Distribution of respondents based on their educational attainment.

Table 4. Factors Exhibiting a Protective Effect against HPV Infection and Associated Diseases.

Factor	OR	CI	P
Age 31–49	0.95	0.78–1.16	0.70
Education (secondary and higher)	0.43	0.17–1.03	0.05
Residence – rural	0.39	0.22–0.73	0.001
Vaccinated against HPV – yes	0.46	0.19–1.00	0.09
Preventive gynecological exams – once or twice a year	0.85	0.49–1.51	0.61
Non-smoker	0.87	0.66–1.14	0.32
No sexual contacts	0.92	0.56–1.50	0.74
Use of contraceptives – yes	0.64	0.36–1.17	0.15
Use of condoms	0.82	0.40–1.68	0.59
Pregnancies – no	0.72	0.47–1.10	0.12
Operative delivery	0.76	0.43–1.33	0.32
No abortions	0.86	0.71–1.03	0.11
No gynecological surgeries	0.82	0.66–1.04	0.07

Discussion

The data analysis showed that 57.0% of the cases were 31–49 years of age. In the control group, the largest percentage distribution (52.0%) was also in the same age group (31–49 years). The study determined that individuals in the age group of 18–30 years had a 1.12 times higher risk of HPV infection (OR = 1.12; 95% CI = 0.64–1.95). According to data from the WHO summarized by the HPV Information Center, the peak spread of HPV infection occurs among women under 25 years of age (Bruni et al. 2023). This finding was supported by Mangieri's study (2023), which concluded that teenagers and sexually active young women are more susceptible to pathogenic infections due to specific cervical anatomy. Mangieri et al. found that women under 25 years old have a 4.92 times higher risk of HPV infection (OR = 4.92; 95% CI = 1.67–14.52; p = 0.004) (Mangieri et al. 2023). Coser et al. (2015) also found a link between HPV infection and younger age, particularly under 30 years old (OR = 2.0; CI = 1.08–3.72; p = 0.028) (Coser et al. 2016). Argyri et al. (2013) identified peaks of HPV prevalence in the age groups 14–19 years (46.6%) and 30–34 years (39.7%) (Argyri et al. 2013). These studies support the conclusion that the age group of 18–30 years increases the risk of HPV infection and associated diseases.

Also, the study identified education as a risk factor for HPV-associated diseases. Participants with primary or lower education (8% of the control group and 19% of the cases) had a 2.35 times higher risk of HPV infection and associated diseases (OR = 2.35; 95% CI = 0.97–5.75). This conclusion is consistent with Yang et al.'s study (2022), which determined that below-average and low education levels were potential risk factors for HPV infection and associated diseases (OR = 1.577; 95% CI = 1.042–2.387) (Yang et al. 2022).

Smoking increases the risk of HPV infection by 1.16 times among exposed individuals. Jing Yang et al.'s study (2020) conducted in China concluded that smoking is a risk factor for high-risk HPV infection. Their data showed that the risk for smokers was 2.254 times higher compared to non-smokers (OR = 2.254; 95% CI: 1.264–4.020) (Yang et al. 2020). Similar results were obtained by Utami et al. (2021), who found that the risk increased by 1.19 times among exposed individuals (OR = 1.19; 95% CI: 0.36–3.91, p = 0.778) (Utami et al. 2021). Mangieri et al. (2023) discovered carcinogenic tobacco compounds in cervical mucus, linking smoking to HPV infection. Their results support the conclusion that smoking increases the risk of HPV-associated diseases (Mangieri et al. 2023).

Only 17.0% of the control group and 9.0% of the cases in our study were vaccinated against HPV. We found that the levels of HPV vaccination among adult women were low. Lack of HPV vaccination was identified as a factor that increases the risk of HPV infection and associated diseases (OR = 2.05; 95% CI: 0.86–4.92; p = 0.11). Naslazi et al. (2021) calculated that the relative risk of cervical cancer in unvaccinated women compared to vaccinated women ranged from 1.7 to 10.8 (Naslazi et al. 2021). Spinner et al. (2019) conducted a logistic regression model that found the risk of infection among unvaccinated women was 1.90 times higher than that of those vaccinated with the 9-valent vaccine (OR = 1.90; 95% CI: 1.09–3.34) (Spinner et al. 2019).

Regular gynecological examinations are crucial for secondary prevention. The percentage distribution of respondents based on the frequency of gynecological visits showed that 42.0% of cases and 37.0% of the control group had annual preventive exams. Concerningly, some respondents only visited a specialist when a problem arose (15.0% of cases and 19.0% of the control group). The study found that having a preventive gynecological exam once or twice a year protects women (OR = 0.85; 95% CI: 0.49–1.51). These findings support the recommendations of the American College of Obstetricians and Gynecologists (ACOG) from 2015, which suggest annual gynecological exams for asymptomatic patients (Guirguis-Blake et al. 2017). Despite ACOG's 2018 recommendation to conduct screenings every three years for patients with normal conventional cytology results, many reproductive-age women still undergo annual gynecological exams, reducing the risk of late diagnosis of HPV-related infections or diseases (American College of Obstetricians and Gynecologists 2018).

Conclusion

Increasing health literacy among the population and improving preventive efforts related to HPV and associated diseases would mitigate the impact of risk factors.

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