Screening for *Human papillomavirus (HPV)* Infection in Women

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A 28-year-old woman visits her gynaecologist for a routine health examination. She had no prior STD infection and her medical history doesn't indicate any significant past diseases. She recently got married, is sexually active with her husband and they use condom inconsistently, and she had three prior sexual partners before her husband. The results from her gynaecologic examination were unremarkable. Is it recommended for this woman to be screened for HPV infection, and if so, how?

The Clinical Problem

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Epidemiology

Human papillomavirus (HPV) infection is caused by a member of the *Papillomaviridae* family, which is a small nonenveloped circular double stranded DNA virus. HPV enters the epithelium by intruding the skin or mucosa and infects basal stem cells. HPV's genome contains seven early phase and two late phase genes which are required for viral propagation and are called *E* genes and *L* genes, respectively (1). Around 180 subtypes have been found for this virus, which have been further categorized into low-risk and high-risk HPV subtypes. The high-risk HPV subtypes may cause various neoplastic changes and cancers, both in males and females with cervical cancer being the most prevalent cancer (2). Among the numerous high-risk subtypes of HPV, HPV types 16 and 18 are the most prevalent carcinogenic types of HPV (3). HPV, chlamydia, trichomoniasis, and genital herpes have the highest prevalence of sexually transmitted infections (STI) in the United States, among which HPV is the most prevalent STI with about 60% of all prevalent and 50% of all incident STIs. Among the 15 to 59-year-old women, more than 24 million were infected, approximately one-half of them were 15 to 24 years old and 3.8 million of them had a new HPV infection (4). In a representative sample of the United State adult population, oral HPV infection had a higher prevalence among African American people and a lower prevalence among Asian American people. Further analysis indicated that these racial differences in the prevalence of HPV infection are likely caused by difference in sexual behaviours (5).

HPV is transmitted through sexual intercourse and its common risk factors include sexual promiscuity, number of sexual partners, inconsistent condom use, early experience of sexual intercourse, and smoking (6, 7). According to one study, the risk of male-to-female transmission of oncogenic types of HPV was greater in comparison with the risk of female-to-male transmission, while the risk of female-to-male transmission was greater for non-oncogenic types (8). Overall, 80% of sexually active women will experience HPV infection over their lifetime (9). However, safer sexual

behaviours, circumcision and consistent condom use are suggested to lessen the risk of HPV infection (7).

Key Clinical Points
• HPV is the most prevalent STI infection with about 60% prevalence despite the unreported cases. • The highest rate of HPV infection is among young women, between the age of 21 and 29. • HPV infection is an important cause of cervical, cervical, anogenital, head and neck, and oesophageal cancers. • Studies report lower incidence of cervical cancer among women who have undergone HPV screening. • Diagnostic tests for HPV infection include; Pap smear, HPV testing, and colposcopy. Self-testing kits have recently been introduced. • HPV screening should be offered to all sexually active women who are older than 21 years of age according to current screening guidelines.

Complications of HPV Infections in Women

HPV penetrates the epithelial cells through micro-wounds and subsequently enters the basal cells of the basal stratum. In normal uninfected epithelia, the cell cycle ceases as the cells leave the basal layer due to nuclei loss in supra-basal layers. However, in HPV infected cells the cycle continues due to viral activities (Figure 1)(10). The differentiation of the keratinocytes takes place in the granular zone of stratified epithelium. This process is closely linked to the life cycle of HPV. Subsequently, infection leads to unchecked proliferation in these sites due to overriding the mechanisms that cease the cell cycle. This state allows for DNA replication of the virus in synchrony with the chromosomal DNA of the host cells. This uncontrolled cellular proliferation in this layer causes chromosomal instability and accumulation of genetic mutations which further leads to premalignant and malignant lesions (11). The two main oncogenes of high-risk HPV types are the E6 and E7 genes. The E6 binds to the p53 protein of the host cell and cause degradation of this protein and subsequently prevent the apoptosis of the infected host epithelial cell. E7 has a similar role by binding to retinoblastoma (Rb) proteins. The HPV-host-genome-integration causes an increased cellular proliferation and an increased risk of malignancy (12, 13). Viral clearance happens in 90% of women with HPV infection, however, in the remaining 10% the infection can persist. This chronic infection can induce E5-, E6-, and E-7-mediated mutations that can further cause the initiation of cancer, and in 1% the virus genome integration (6).

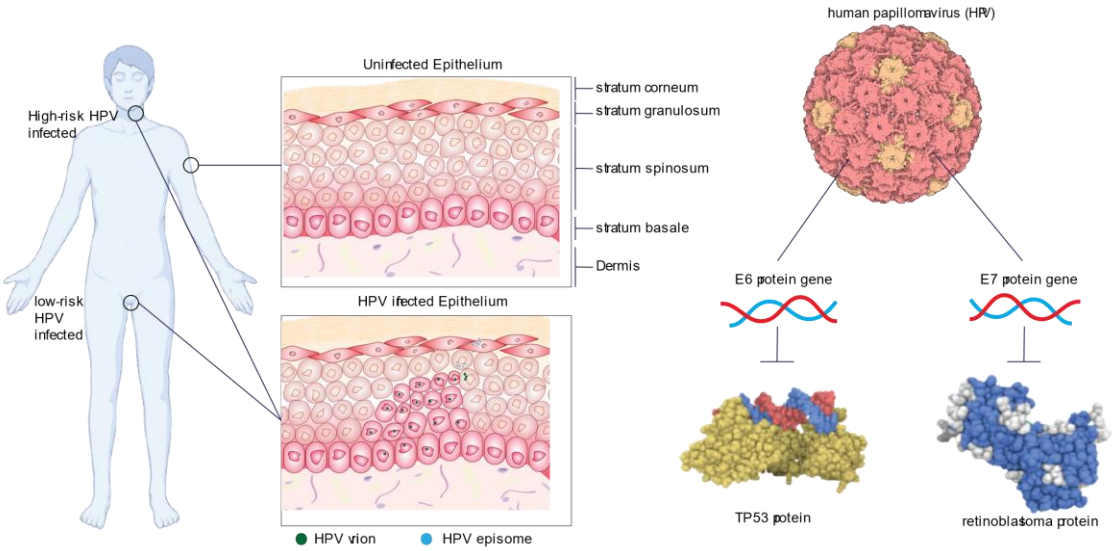

Figure 1. Pathogenesis of HPV

The low-risk HPVs are hardly found to cause cancers and neoplasms. In some cases, HPV may be the underlying cause of papillomatosis in immunodeficient individuals (14). However, twelve HPV types are recognized to be the high-risk carcinogenic HPV types, among which type 16 is the most prevalent (15, 16). HPV can cause cervical, anogenital, oral, oesophageal, and ophthalmologic and breast carcinomas (6). Two cervical lesions are caused by HPV: low-grade squamous intraepithelial lesions (LSIL) and high-grade squamous intraepithelial lesions (HSIL). The type of these cervical lesions is highly correlated with the expression level of E6 and E7. Lower degree of expression occurs in low-grade lesions in basal cells whereas higher degrees of expression occur in high-grade lesions throughout the epithelium. In HSILs, there's a greater chance for integration of HPV DNA with host-cell chromosome, thus greater risk of malignancy (13, 17). Environmental factors can greatly contribute to genomic instability. Studies have shown that alcohol consumption and smoking along with the use of contraceptive hormones and co-infection by other oncogenic viruses such as HIV (human immunodeficiency virus increases the chance of cervical cancer (18-20). Despite the high prevalence of HPV infections, most cervical infections are asymptomatic and transient, of which 70% resolve within one year (21). HPV oncogenic test can be performed to determine the risk of cervical intraepithelial neoplasia (CIN) that may range from CIN-I to CIN-III. CIN-I is an LSIL whereas CIN-II and III are considered high-grade dysplasia or HSIL (22, 23). A negative oncogenic HPV test implies lower chance of CIN-III, while a positive test implies higher risks. One cohort study showed, that women with positive test at baseline and 2 years later (means they had persistent infection), had an absolute risk of CIN-III at 12 years (24). The transition of persistent infection takes several years or decades. The peak of HPV infection incidence happens at the age of 20, the peak incidence of CIN-III at the age of 30, and the peak of cervical cancer in the 40s (22, 25). This highlights the importance of prevention via HPV screening in young females.

Strategies and Evidence

Evaluation

Exposure to HPV through vaginal, anal, or oral sexual intercourse typically causes and infection that may progress to clinically apparent lesions, such as genital warts and CIN lesions of the lower genital tract (26). The low-risk cutaneous types of HPV cause common warts and flat warts (27, 28), while the mucosal types, despite their name, cause cutaneous genital lesions and typically do not cause

neoplasia (29). These lesions are due to the stimulation of epithelial cells for excessive proliferation (30). The infection will usually resolve within two years, however, some high-risk infections may persist and cause further complications (26).

Screening to Reduce Complications of HPV

HPV infection along with cervical carcinoma causes a noticeable global burden. Also, studies related to HPV detection and treatment are key factors in diminishing this huge burden globally. Screening women for HPV and cervical dysplasia can significantly reduce their risk of death from malignancies (31). In a 10-year randomized controlled trial in Germany, HPV screening resulted in a noticeable decrease in the incidence of cervical cancer. In this study, 26,624 non-hysterectomised women who were at least 30 years old underwent co-testing with Papanicolaou smear and high-risk HPV DNA testing. The next screening session of women with normal results was 5 years later and those with HPV positive tests or abnormal Pap smear findings were referred for colposcopy instantly. Women with incongruous results repeated their test after one year and those with persistent positive results were referred for colposcopy. 274 cases were diagnosed with CIN-III among which 270 cases had positive and 4 cases had negative HPV test. 31 cases had invasive cervical cancer among which 29 cases had positive and 2 cases had negative HPV test. Between the first round and the subsequent rounds, a noticeable decrease of the five-year incidence of CIN-III (0.96% to 0.16%) and cervical cancer (0.10% to 0.025%) were observed. Around 90% (246 pf 274 cases) of CIN-III were diagnosed with the first colposcopy. The decrease of disease incidence was related to HPV testing because, among the HPV negative and Pap smear positive women, no CIN-III occurred (32). In a similar study in the United States, from 1976 to 2009 there was a noticeable decline of the incidence (cases per 100,000 women) of early-stage cervical cancer (9.8 to 4.9) and late-stage cervical cancer (5.3 to 3.7) due to screening (33).

Screening Recommendations for HPV

Screening Methods

Cervical cancer, the most severe consequence of HPV infection, is the third most prevalent cancer in women globally and the first cause of cancer death among women in developing countries. However, timely screening can dramatically reduce this burden. There are two major screening methods for HPV or cervical cancer screening; liquid-based cytology (LBC) or Papanicolaou smear (Pap smear) and HPV-DNA testing (31). The endocervical swabs are usually collected during a routine vaginal speculum

Table 2. Indications for HPV screening

≥ 21 and ≤ 65
sexually active
multiple sexual partners
inconsistent condom use
sexual contact with a partner with a prior STD

examination for both tests. The cytology test examines the presence of precancerous or cancerous cells among the cervical cells (34). There are several tests that have been FDA-approved for HPV-DNA testing. Since Papanicolaou smear has high specificity (98%) and lower sensitivity (55-80%), the FDA approved the combination of HPV-DNA testing and cytology or co-testing for cervical cancer screening. Due to the higher prevalence of high-risk HPV infection among young women and the risk of unnecessary overtreatment, screening via HPV testing is not approved for women under 30. HPV-DNA testing may be performed on a specimen that was collected separately or on the remaining cytology specimen. The co-testing can result in increasing the sensitivity of the Papanicolaou smear from 55-85% to approximately 100%. Further information regarding the sensitivity and specificity of HPV screening is summarized in Table 1. For women with negative results for both tests, screening is

performed every 5 years. According to the current guidelines, 21 to 29 years old women should be screened only with pap smear every 3 years (31). 30 to 65 years old women have three options according to USPSTF (the United States Preventive Services Task Force) guidelines. They can undergo HPV testing every 5 years, Papanicolaou smear every 3 years or co-testing every 5 years (34). Positive results of HPV testing or abnormal results of Papanicolaou smear are referred for colposcopy for confirmation and definitive diagnosis (35). Recently, mailed self-sample HPV testing kits are designed for women who are unable or unwilling to participate in a periodic clinic-based screening. These kits are currently under clinical trials, however, if approved, they can ease the process of screening for women at high risk of infection (36).

Table 1. Diagnostic Accuracy of HPV tests

Test Comparison		Pooled Sensitivity (95% CI)	Pooled Specificity
HPV test compared with VIA	HPV test	95% (84-98)	84% (72-91)
	VIA test	69% (54-81)	87% (79-92)
VIA compared with cervical smear	VIA test	77% (65-85)	82% (67-91)
	Cervical smear	84% (76-90)	88% (79-93)
HPV test compared with cervical smear	HPV test	94% (89-97)	90% (86-93)
	Cervical smear	70% (57-80)	95% (92-97)
HPV test (from comparisons)		94% (89-97)	88% (84-92)

from the analysis performed by Mustafa et al.(37)

Cost-Effectiveness of Screening

According to one study, model predictions indicate that the most cost-effective strategy in cervical cancer and HPV screening is primary high-risk HPV testing (HR-HPV), due to cost reduction and also increase the detection of CIN-II or III. However, HR-HPV testing is somehow problematic because of its high sensitivity and its low specificity, which may subsequently cause overtreatment. Recently the concept of dual staining has been proposed to reduce overtreatment. Literature review indicates that across all age groups, dual stating had significant higher sensitivity than cytology while having equal specificity (38, 39).

HPV Screening in Pregnant Women

Apart from high-risk HPV infection, high parity and younger age at first full-term pregnancy are co-factors that are associated with cervical cancer (40). Also, several studies indicated that the prevalence of HPV infection increases during pregnancy and clearance of HPV infection takes more time. This may be due to hormonal changes and decreased immunity during pregnancy (41). A recent systematic review and meta-analysis study have shown that there is a strong association between HPV infection and preterm birth and preterm premature rupture of membranes (PPROM). HPV infection may also be associated with infant low-birth-weight, foetal growth restrictions and foetal death (42). Current guidelines (43) haven't included HPV screening for pregnant women, unlike other STDs like C*hlamydia trachomatis* or *Neisseria gonorrhoeae.* However, these guidelines should be updated according to the latest literature regarding screening recommendations for special populations like pregnant women.

Treatment

Currently, there is no cure no treatment for the virus itself and subclinical HPV infection usually clears spontaneously. However, genital warts and precancerous lesions can be treated. Antiviral therapy is not specifically indicated to treat HPV infection (43). Also, viral latency, high reinfection and recurrence rate along with the basal layer reservoir reduce the success rates of treating this infection and emphasizes on prolonged treatment cycles. Benign HPV lesions can be removed either by thermal, electrical, or chemical means (44). Chemical therapy for skin or genital warts involves three methods; podophyllin compounds, trichloroacetic acid, and imiquimod. Trichloroacetic acid is safe to use during pregnancy, however, podophyllin acts by blocking cell division and cannot be used during pregnancy. Imiquimod compounds stimulate tumour necrosis factor (TNF) and interferons (IFN) production. Studies indicate that imiquimod can decrease high-risk HPV infection (44, 45). Cryotherapy is freezing the lesion via liquid (nitrogen) or metal (cryoprobe) agents which subsequently causes cell death (46). Resistant or extensive lesions can be removed via electrocautery or surgical excision under local, regional, or general anaesthesia and cervical lesions can be removed by a loop electrosurgical excision procedure (44). Precancerous lesions should be detected through screening and managed based on existing guidance (43). Vaccination is a key factor in mitigating the HPV infection consequences, cervical and other types of cancers. Currently, there are three FDA-approved vaccines available for prevention of HPV infection; 9-valent and quadrivalent HPV vaccine (Gardasil), and bivalent HPV vaccine (Cervarix). A recent review on efficacy of HPV vaccines indicated that Cervarix induces high antibody titres against high-risk HPV types 16 and 18 and can prevent the incidence of HPV infection for 10 years or more. Also, quadrivalent Gardasil have shown excellent efficacy against cervical HPV infections, genital warts, and cancer precursor lesions. Finally, Gardasil-9 have also shown high efficacy in prevention of infections and cervical cancer precursor lesions related to certain types of HPV (47).

Table 3. HPV screening recommendations for sexually active women

	2020 ACS	**2012 ACS**	**2018 USPSTF**
Age 21–24	No screening	Pap smear every 3 years	Pap smear every 3 years
Age 25–29	HPV test every 5 years (preferred)/ HPV/Pap co-testing every 5 years (acceptable) /Pap smear every 3 years (acceptable)	Pap smear every 3 years	Pap smear every 3 years
Age 30–65	HPV test every 5 years (preferred) / HPV/Pap co-testing every 5 years (acceptable) / Pap smear every 3 years (acceptable)	HPV/Pap co-testing every 3 years (preferred) / Pap smear every 3 years (acceptable)	Pap smear every 3 years, HPV test every 5 years, or HPV/Pap co-testing every 5 years
Age 65 and older	No screening if a series of prior tests were normal	No screening if a series of prior tests were normal	No screening if a series of prior tests were normal and not at high risk for cervical cancer

ACS, American Cancer Society; USPSTF, United States Preventive Services Task Force
based on ACS's update on screening guidelines (48)

Areas of Uncertainty

Several studies have indicated that although screening and vaccination have taken place in the last decade, incidence of HPV-related cancers is still increasing in several high- and low-income countries. One study that projected the cancer incidence attributable to HPV infection to 2030 by the data of cancer incidence from 1990 to 2012. According to this study the cancer incidence will face an increasing trend during this period (49, 50). The focus on vaccination of women can be a potential reason for this pattern. HPV is transmitted by contact between partners and vaccination of females at the age of 13 to 26 is recommended, however, lack of focus on male vaccination in this age may increase the incidence. Further research regarding men's knowledge about HPV complications and vaccination should investigate viable strategies to mitigate this problem.

Although current guidelines suggest screening every 3 years for 21 to 29 years old women, the most effective screening interval for at-risk women is unknown. Missing the screening in this time frame can further increase the chance of persistent HPV infection and subsequent cervical cancer. Also, data is lacking regarding the benefits of shorter screening period and HPV screening of women at low-risk. Current guidelines indicate HPV screening for women. Data is lacking regarding the male screening effect in reducing HPV infection incidence. Currently, there is no FDA-approved tests for HPV in men. Screening for anal, penile, or oropharyngeal cancers is not recommended by CDC guideline (51).

Guidelines

According to USPSTF, which divides women in three groups for screening, 21 to 29 years old women should undergo Pap smear testing every three years, and 35 to 65 years old women either HPV test every 5 years, co-testing every 5 years, or Pap smear test every 3 years. Further information regarding different guidelines recommendations for screening is summarized in Table 3 and relative algorithm in Figure 2.

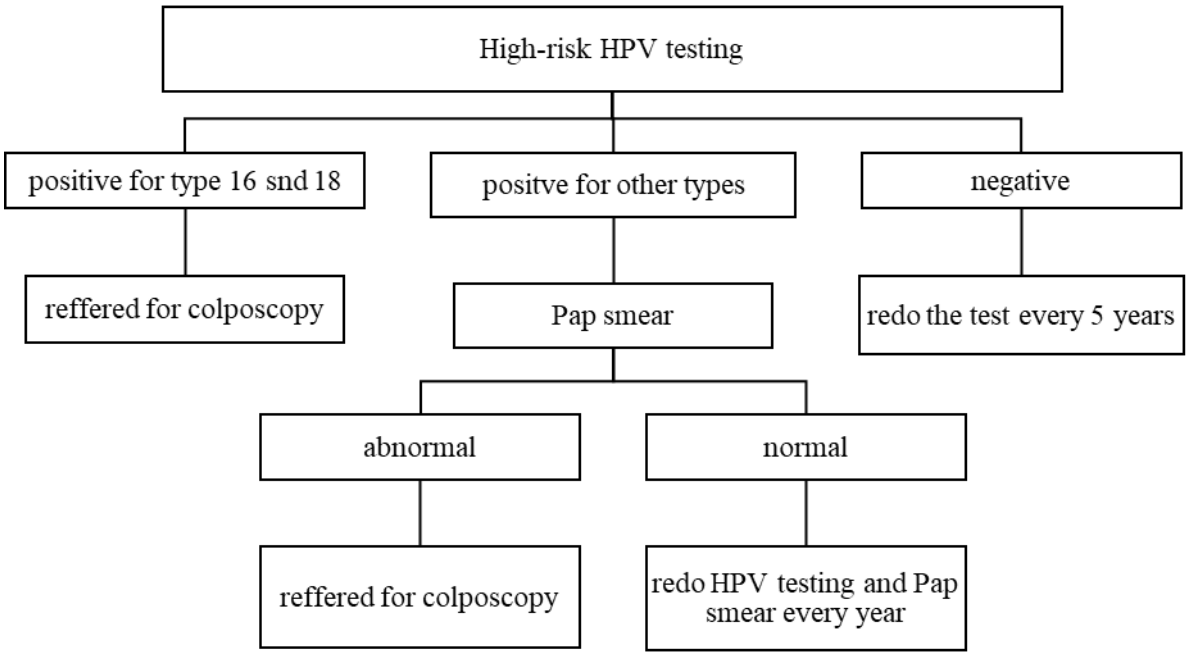

Figure 2. HPV screening algorithm for HR-HPV

Summary and Recommendations

HPV screening is recommended for the women depicted in our case vignette because her age is between 21 and 29, is currently sexually active, had several prior sexual partners, and uses condom inconsistently. Also, assessment of STDs risk factors and counselling on safer sex is recommended for this woman. For obtaining higher sensitivity and specificity, co-testing of Papanicolaou smear along with HPV testing. If the patient gets a positive result, she should be referred for colposcopy for further definitive diagnosis and treatment plan. Also, her sexual partners should be alarmed for HPV infection and HPV screening. If she tested negative and haven't been vaccinated, vaccination is recommended to reduce the risk of HPV infection for herself and her husband.

References

1. Groves IJ, Coleman N. Pathogenesis of human papillomavirus-associated mucosal disease. J Pathol. 2015;235(4):527-38.
2. Nunes EM, Talpe-Nunes V, Sichero L. Epidemiology and biology of cutaneous human papillomavirus. Clinics (Sao Paulo). 2018;73(suppl 1):e489s.
3. Muñoz N, Bosch FX, de Sanjosé S, Herrero R, Castellsagué X, Shah KV, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med. 2003;348(6):518-27.
4. Kreisel KM, Spicknall IH, Gargano JW, Lewis FMT, Lewis RM, Markowitz LE, et al. Sexually Transmitted Infections Among US Women and Men: Prevalence and Incidence Estimates, 2018. Sex Transm Dis. 2021;48(4):208-14.
5. Choi JS, Tang L, Yu AJ, Swanson MS, Chambers TN, Kokot NC, et al. Prevalence of oral human papillomavirus infections by race in the United States: An association with sexual behavior. Oral Dis. 2020;26(5):930-40.
6. Araldi RP, Sant'Ana TA, Módolo DG, de Melo TC, Spadacci-Morena DD, de Cassia Stocco R, et al. The human papillomavirus (HPV)-related cancer biology: An overview. Biomed Pharmacother. 2018;106:1537-56.
7. Rodríguez-Álvarez MI, Gómez-Urquiza JL, Husein-El Ahmed H, Albendín-García L, Gómez-Salgado J, Cañadas-De la Fuente GA. Prevalence and Risk Factors of Human Papillomavirus in Male Patients: A Systematic Review and Meta-Analysis. Int J Environ Res Public Health. 2018;15(10).
8. Liu M, He Z, Zhang C, Liu F, Liu Y, Li J, et al. Transmission of genital human papillomavirus infection in couples: a population-based cohort study in rural China. Sci Rep. 2015;5:10986.
9. Tommasino M. The human papillomavirus family and its role in carcinogenesis. Semin Cancer Biol. 2014;26:13-21.
10. Longworth MS, Laimins LA. Pathogenesis of human papillomaviruses in differentiating epithelia. Microbiol Mol Biol Rev. 2004;68(2):362-72.
11. Miller DL, Puricelli MD, Stack MS. Virology and molecular pathogenesis of HPV (human papillomavirus)-associated oropharyngeal squamous cell carcinoma. Biochem J. 2012;443(2):339-53.
12. Hausen Hz. Papillomaviruses Causing Cancer: Evasion From Host-Cell Control in Early Events in Carcinogenesis. JNCI: Journal of the National Cancer Institute. 2000;92(9):690-8.
13. Scheurer ME, Tortolero-Luna G, Adler-Storthz K. Human papillomavirus infection: biology, epidemiology, and prevention. Int J Gynecol Cancer. 2005;15(5):727-46.
14. Doorbar J, Quint W, Banks L, Bravo IG, Stoler M, Broker TR, et al. The biology and life-cycle of human papillomaviruses. Vaccine. 2012;30 Suppl 5:F55-70.
15. Muñoz N, Castellsagué X, Berrington de González A, Gissmann L. Chapter 1: HPV in the etiology of human cancer. Vaccine. 2006;24 Suppl 3:S3/1-10.
16. Bouvard V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, et al. A review of human carcinogens--Part B: biological agents. Lancet Oncol. 2009;10(4):321-2.
17. Ault KA. Epidemiology and natural history of human papillomavirus infections in the female genital tract. Infect Dis Obstet Gynecol. 2006;2006 Suppl:40470.
18. Moscicki AB, Schiffman M, Burchell A, Albero G, Giuliano AR, Goodman MT, et al. Updating the natural history of human papillomavirus and anogenital cancers. Vaccine. 2012;30 Suppl 5(0 5):F24-33.
19. Smith JS, Green J, Berrington de Gonzalez A, Appleby P, Peto J, Plummer M, et al. Cervical cancer and use of hormonal contraceptives: a systematic review. Lancet. 2003;361(9364):1159-67.
20. Moreno V, Bosch FX, Muñoz N, Meijer CJ, Shah KV, Walboomers JM, et al. Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infection: the IARC multicentric case-control study. Lancet. 2002;359(9312):1085-92.

21. Winer RL, Hughes JP, Feng Q, Xi LF, Cherne S, O'Reilly S, et al. Early natural history of incident, type-specific human papillomavirus infections in newly sexually active young women. Cancer Epidemiol Biomarkers Prev. 2011;20(4):699-707.
22. Wang CJ, Palefsky JM. Human Papillomavirus (HPV) Infections and the Importance of HPV Vaccination. Curr Epidemiol Rep. 2015;2(2):101-9.
23. Chan CK, Aimagambetova G, Ukybassova T, Kongrtay K, Azizan A. Human Papillomavirus Infection and Cervical Cancer: Epidemiology, Screening, and Vaccination-Review of Current Perspectives. J Oncol. 2019;2019:3257939.
24. Sundström K, Eloranta S, Sparén P, Arnheim Dahlström L, Gunnell A, Lindgren A, et al. Prospective study of human papillomavirus (HPV) types, HPV persistence, and risk of squamous cell carcinoma of the cervix. Cancer Epidemiol Biomarkers Prev. 2010;19(10):2469-78.
25. Cuzick J, Arbyn M, Sankaranarayanan R, Tsu V, Ronco G, Mayrand M-H, et al. Overview of human papillomavirus-based and other novel options for cervical cancer screening in developed and developing countries. Vaccine. 2008;26:K29-K41.
26. Juckett G, Hartman-Adams H. Human papillomavirus: clinical manifestations and prevention. Am Fam Physician. 2010;82(10):1209-13.
27. Hsueh PR. Human papillomavirus, genital warts, and vaccines. J Microbiol Immunol Infect. 2009;42(2):101-6.
28. Bernard HU, Burk RD, Chen Z, van Doorslaer K, zur Hausen H, de Villiers EM. Classification of papillomaviruses (PVs) based on 189 PV types and proposal of taxonomic amendments. Virology. 2010;401(1):70-9.
29. Middleton K, Peh W, Southern S, Griffin H, Sotlar K, Nakahara T, et al. Organization of human papillomavirus productive cycle during neoplastic progression provides a basis for selection of diagnostic markers. J Virol. 2003;77(19):10186-201.
30. Nowakowski A, Kotarski J. [Clinical manifestations of HPV infections]. Ginekol Pol. 2007;78(9):709-14.
31. Bedell SL, Goldstein LS, Goldstein AR, Goldstein AT. Cervical Cancer Screening: Past, Present, and Future. Sex Med Rev. 2020;8(1):28-37.
32. Horn J, Denecke A, Luyten A, Rothe B, Reinecke-Lüthge A, Mikolajczyk R, et al. Reduction of cervical cancer incidence within a primary HPV screening pilot project (WOLPHSCREEN) in Wolfsburg, Germany. British Journal of Cancer. 2019;120(10):1015-22.
33. Yang DX, Soulos PR, Davis B, Gross CP, Yu JB. Impact of Widespread Cervical Cancer Screening: Number of Cancers Prevented and Changes in Race-specific Incidence. Am J Clin Oncol. 2018;41(3):289-94.
34. Institute NC. Understanding abnormal HPV and Pap smear test results 2021 [updated January 13, 2021. Available from: https://www.cancer.gov/types/cervical/understanding-abnormal-hpv-and-pap-test-results#hpv-test-and-pap-test.
35. Medicine JH. Colposcopy 2021 [Available from: https://www.hopkinsmedicine.org/health/treatment-tests-and-therapies/colposcopy.
36. Montealegre JR, Anderson ML, Hilsenbeck SG, Chiao EY, Cantor SB, Parker SL, et al. Mailed self-sample HPV testing kits to improve cervical cancer screening in a safety net health system: protocol for a hybrid effectiveness-implementation randomized controlled trial. Trials. 2020;21(1):872.
37. Mustafa RA, Santesso N, Khatib R, Mustafa AA, Wiercioch W, Kehar R, et al. Systematic reviews and meta-analyses of the accuracy of HPV tests, visual inspection with acetic acid, cytology, and colposcopy. International Journal of Gynecology & Obstetrics. 2016;132(3):259-65.
38. Tjalma WAA. Diagnostic performance of dual-staining cytology for cervical cancer screening: A systematic literature review. Eur J Obstet Gynecol Reprod Biol. 2017;210:275-80.
39. Tantitamit T, Khemapech N, Havanond P, Termrungruanglert W. Cost-Effectiveness of Primary HPV Screening Strategies and Triage With Cytology or Dual Stain for Cervical Cancer. Cancer Control. 2020;27(1):1073274820922540.
40. Schmeink CE, Melchers WJ, Hendriks JC, Quint WG, Massuger LF, Bekkers RL. Human papillomavirus detection in pregnant women: a prospective matched cohort study. J Womens Health (Larchmt). 2012;21(12):1295-301.
41. Pandey D, Solleti V, Jain G, Das A, Shama Prasada K, Acharya S, et al. Human Papillomavirus (HPV) Infection in Early Pregnancy: Prevalence and Implications. Infectious Diseases in Obstetrics and Gynecology. 2019;2019:4376902.
42. Niyibizi J, Zanré N, Mayrand MH, Trottier H. Association Between Maternal Human Papillomavirus Infection and Adverse Pregnancy Outcomes: Systematic Review and Meta-Analysis. J Infect Dis. 2020;221(12):1925-37.
43. Workowski KA, Bolan GA. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015;64(Rr-03):1-137.

44. Hathaway JK. HPV: diagnosis, prevention, and treatment. Clin Obstet Gynecol. 2012;55(3):671-80.
45. Tyring SK, Arany I, Stanley MA, Tomai MA, Miller RL, Smith MH, et al. A randomized, controlled, molecular study of condylomata acuminata clearance during treatment with imiquimod. J Infect Dis. 1998;178(2):551-5.
46. Chumworathayi B, Thinkhamrop J, Blumenthal PD, Thinkhamrop B, Pientong C, Ekalaksananan T. Cryotherapy for HPV clearance in women with biopsy-confirmed cervical low-grade squamous intraepithelial lesions. Int J Gynaecol Obstet. 2010;108(2):119-22.
47. Cheng L, Wang Y, Du J. Human Papillomavirus Vaccines: An Updated Review. Vaccines (Basel). 2020;8(3).
48. National-Cancer-Institute. ACS's Updated Cervical Cancer Screening Guidelines Explained 2020 [updated September 18, 2020. Available from: https://www.cancer.gov/news-events/cancer-currents-blog/2020/cervical-cancer-screening-hpv-test-guideline.
49. Wu J, Xiao F, Zheng Y, Lin Y, Wang H-L. Worldwide trend in human papillomavirus–attributable cancer incidence rates between 1990 and 2012 and Bayesian projection to 2030. Cancer.n/a(n/a).
50. Hansen BT, Campbell S, Nygård M. Long-term incidence trends of HPV-related cancers, and cases preventable by HPV vaccination: a registry-based study in Norway. BMJ Open. 2018;8(2):e019005.
51. Control CfD. HPV and Men - Fact Sheet. Centers for Disease Control and Prevention. 2021.