REVIEW

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Human Papillomavirus as Non-Traditional Cardiovascular Risk Factor: Fact or Fiction? Part 1

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ABSTRACT

Human papillomavirus (HPV) is the most common sexually transmitted infection in the United States and worldwide, with more than 42 million Americans infected with types of HPV that are known to cause disease. Although the link between HPV and the development of a variety of cancers has been strongly established, recent literature has demonstrated a potential association between HPV and increased risk of cardiovascular disease. Nevertheless, despite plausible mechanisms for the development of cardiovascular disease with HPV infection, a causative relationship has yet to be firmly established, in part due to potential confounding risk factors between the two. In this 2-part series, we discuss the emerging relationship between HPV and cardiovascular disease. In part 1, we focus on the pathophysiology of HPV infection and potential mechanisms for the development of cardiovascular disease.

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INTRODUCTION

Human papillomavirus (HPV) is a double-stranded non-enveloped deoxyribonucleic acid (DNA) virus that belongs to the Papillomaviridae virus family. It is the most common sexually transmitted infection in the United States and worldwide, with approximately 14 million new HPV infections occurring annually in the United States.[1] More than 200 HPV types have been identified, and these types can be categorized based on their carcinogenic properties (high-risk and low-risk HPV types) and tissue tropism (cutaneous vs mucosal).[2] Around 90% of HPV infections are cleared or become inactive within 12-24 months of exposure without any intervention.[3] However, infection with high-risk HPV types is more likely to persist, and as a result, increase risk for disease. Although the link between HPV and the development of a variety of cancers has been strongly established, recent literature has demonstrated a potential link between HPV and cardiovascular disease. In this comprehensive 2-part series, we discuss the pathophysiology of HPV and cardiovascular disease, current prevention and treatment strategies, and the future direction of the literature.

Mechanism of Human Papillomavirus Infection

The HPV genome consists of an icosahedral capsid of about 60 nm in diameter, containing a single molecule of double-stranded circular DNA of approximately 8000 base pairs.[4] Only 1 strand of the double-stranded DNA genome is used as a template for transcription and this coding strand contains 3 genomic regions, including approximately 10 open reading frames.[4] The genome contains 3 regulatory proteins (E1, E2, and E4) and 3 oncoproteins (E5, E6, and

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E7) encoded in 4000 base pairs that participate in viral replication and transformation of cells.[2] The late region of the genome encodes the major (L1) and minor (L2) capsid proteins.[4] Human papillomavirus shows a marked tissue tropism, first infecting undifferentiated basal epithelial cells in squamous stratified epithelia, and then viral progeny are produced in differentiated daughter cells in the uppermost epithelial layers.[4] Virions bind initially to heparan sulfate proteoglycans, which serve as primary attachment receptors on basal cells or exposed basement membrane resulting from epithelial trauma or permeabilization.[4] Internalization of capsids from the cell surface is asynchronous and can take approximately 2 to 4 hours, with some capsids remaining on the surface much longer than others.[4] The virus is ultimately endocytosed through a potentially novel mechanism, similar to micropinocytosis, that is clathrin-, caveolin-, and lipid-raft independent.[4] Following endocytosis, virions are then transported through the endosomal system where they undergo further structural changes that result in partial uncoating, leading to dissociation of L1 from the genome complex.[4] Microtubules aid in the movement of the virus through the cytoplasm to the nucleus, and entry of the viral genome into the nucleus requires mitosis, a process mediated by L2. Once the genome has entered the nucleus, L2 and the genome colocalize at ND10 domains, which is a critical step in the establishment of infection and allows for transcription of the viral genome.[4]

Following infection, initial genome amplification occurs prior to maintenance of the viral genome in the nuclei of infected basal epithelial cells.[4] Viral genomes replicate once per cell cycle, on average, during S phase, ensuring persistent infection of basal cells.[4] The latter is described as the "latent" phase of the viral lifecycle, where HPV genomes are thought to persist in basal epithelial cells for years to decades. During this period of time, however, a switch from stable replication to vegetative viral DNA replication must occur to allow the production of genomes for packaging into virions.[4] This step is predicated on the viral proteins E1 and E2. Human papillomaviruses do not encode any other replication enzymes and must hijack the host DNA synthesis machinery to accomplish replication of the viral genome.[4] E1 and E2 recruit cellular DNA polymerases and other essential accessory enzymes to enable viral genome replication. These proteins further contribute to the viral lifecycle by driving cell proliferation in the basal and parabasal layers, causing an increase in the size of the initial infected area.[4] E6, known to inactivate the p53 tumor suppressor, not only upregulates telomerase activity, but also blocks the pro-apoptotic activities of p53 in response to DNA damage and cellular stress caused by aberrant S-phase entry.[4] E7, on the other hand, is known to target retinoblastoma tumor suppressor RB1 and results in constitutive activation of E2F modulated gene expression programs that control DNA synthesis and cell proliferation.[4] Through these mechanisms, HPV ultimately induces a DNA damage response.

Completion of the viral lifecycle involves cell cycle exit and expression of L1 and L2 to allow for genome packaging.[4] Maturation is then based upon the accumulation of disulfide bonds between L1 proteins, resulting in condensation of the capsid and increasing its stability and resistance to proteolytic digestion. The final component of HPVs viral lifecycle is viral shedding. Human papillomaviruses are non-lytic, and as a consequence, viral shedding occurs due to normal loss of nuclear and cytoplasmic integrity during terminal differentiation of the infected keratinocyte.

CLINICAL SIGNIFICANCE

- A causative relationship between cardiovascular disease and human papillomavirus infection has yet to be firmly established.
- Among patients with pre-established cardiovascular disease, human papillomavirus status further increases risk of major adverse cardiovascular events.
- Human papillomavirus status among patients with pre-established cardiovascular disease would warrant more aggressive risk factor modification.
- All studies to date describing the association between human papillomavirus infection and cardiovascular disease have focused exclusively on females; whether such an association pertains in males remains largely unstudied.

Pathogenesis of Human Papillomavirus-Related Cardiovascular Disease

Human papillomavirus is considered a tissue-specific virus with a strong tropism toward basal epithelial cells of stratified squamous epithelia. The latter is supported by years of research that illuminated the potential of HPV to induce squamous cell carcinomas and adenocarcinomas with metastatic ability, in particular anogenital cancers and a growing proportion of oropharyngeal cancers.[5] Given its mechanism, other tissues in the human body, including blood vessels, were long believed to be incapable of supporting HPV viral replication.

Since the first report of the potential correlation between HPV infection and risk of cardiovascular disease by Kuo and Fujise in 2011,[5] additional studies have supported this association (Table). Despite the current literature being sparse in the investigation of its pathogenetic effect, with various hypotheses having been described, it is possible that HPV increases the risk for cardiovascular disease by promoting atheroma development via the induction of systemic inflammation, or by directly targeting the vasculature.[5]

Human papillomavirus is able to modulate signaling through the nuclear factor kappa-light-chain-enhancer of activated B-cells (NFκB), a critical driver of inflammation. The nuclear factor kappa-light-chain-enhancer of activated

Table Studies Investigating the Relationship Between Human Papillomavirus and Cardiovascular Disease

Study	Year	Country	Population	No. of Patients	Mean Age	Median Follow-up	Findings
Kuo and Fujise[6]	2011	United States	Females aged 20-59 years in NHANES	2450	37.9 years	N/A	Presence of vaginal HPV DNA associated with CVD (OR 2.3, 95% CI 1.27-4.16) after adjustment for several confounders. OR of CVD in females with oncogenic HPV types compared with those with negative HPV was 2.86 (95% CI 1.43-5.7).
Lawson et al[7]	2015	Australia	20 donors whose cause of death was determined to be a myocardial infarction by pathology	20	46.3 years	N/A	HPV types 16 and 18 identified in 55% of atheromatous coronary arteries.
Joo et al[8]	2019	South Korea	Females aged ≥ 30 years who underwent a comprehensive health exam from 2011 to 2016 at Kangbuk Samsung Hospital Total Healthcare Centers between 2011 to 2016	63,411	39.7 years	4.4 years	Significant association between high-risk HPV infection and incident CVD (multivariable-adjusted HR 1.25, 95% CI 1.03-1.52). Risk of incident CVD higher among patients with obesity (*P* value for interaction .02) and metabolic syndrome (*P* value for interaction .05).
Brito et al[9]	2019	Brazil	Females aged ≥ 35 and climacteric	52	N/A	N/A	Presence of cervical HPV was strongly associated with CAD, after adjusting for demographic variables, health and sexual behaviors, comorbidities, and known cardiovascular risk factors. HPV-positive females showed a greater likelihood of having CAD (OR 3.74, 95% CI 1.16-11.96) as compared with HPV-negative females, particularly those infected with high-risk HPV types (OR 4.90, 95% CI 1.26-19.08).
Liang et al[10]	2023	United States	Females aged 20-59 years in NHANES 2003-2016	9353	38.25 years in HPV (+), 40.81 years in HPV (-)	N/A	Presence of cervical-vaginal HPV infection associated with CVD even after adjustment for confounding variables (OR 1.54, 95% CI 1.15-2.08). This association was absent among those vaccinated against HPV (OR 0.50, 95% CI 0.07-3.51) but present among those who were not vaccinated (OR 1.63, 95% CI 1.18-2.25).
Cheong et al[11]	2024	South Korea	Females aged ≥ 30 years who underwent a health examination at Kangbuk Samsung Hospital Total Healthcare Centers between 2004-2018	163,250	40.2 years	8.6 years	Increased rates of CVD death among patients with high-risk HPV infection (adjusted HR for ASCVD death 3.91, 95% CI 1.85-8.26). Association between high-risk HPV infection and ASCVD mortality stronger in females with obesity (*P* value for interaction .006).

ASCVD = atherosclerotic cardiovascular disease; CAD = coronary artery disease; CI = confidence interval; CVD = cardiovascular disease; DNA = deoxyribonucleic acid; HPV = human papillomavirus; HR = hazard ratio; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio.

B-cells is a nuclear transcription factor that controls the expression of a vast number of genes involved in inflammation, cell proliferation, metabolism, differentiation and apoptosis, and its activation is able to elicit all the hallmarks of cancer.[12] It may be activated by the HPV16 E6 oncoprotein, resulting in the up-regulation of transcription of downstream genes (eg, cIAP2).[13] E6 was also suggested to inhibit the NFκB inhibitor X-box binding 1, further up-regulating NFκB signaling.[14] Through this pathway, lesions induced by HPV can be characterized by chronic inflammatory phenomena.[5] The latter is further supported by Kemp et al, [15] who demonstrated that older females with persistent HPV infection of the uterine cervix were shown to have elevated levels of pro-inflammatory cytokines. In addition, the E6 oncoprotein has been shown to degrade the tumor-suppressor protein p53, which plays a role in the development of atherosclerosis.[16] This correlation was supported by Zekavat et al,[17] who were able to demonstrate through whole-exome sequencing a direct causal contribution of TP53 mutations to atherosclerosis. Notably, the accelerated atherosclerosis observed with p53 mutants seems mainly related to increased cellular proliferation, leading to an increase in macrophage burden in atherosclerotic plaques.[17] Consequently, persistent HPV infection causing inactivation of p53 may directly influence the development of atherosclerosis. Human papillomavirus has also been shown to be able to induce the systemic up-regulation of pro-inflammatory cytokines such as interleukin-6, tumor necrosis factor alpha, and interleukin-1B, which not only contribute to an inflammatory state, but may then result in endothelial damage.[5] In addition, Kim et al[18] were able to demonstrate that the HPV 16 E5 oncoprotein increased vascular endothelial growth factor (VEGF) mRNA and protein expression in various cell types, and the effect of E5 on the enhancement of VEGF expression is mediated through increased transcriptional activity by the activation of the EGFR signaling pathway. In correlation, the VEGF family governs functions including promoting tumor angiogenesis, and may play a role in interfering with lipid metabolism and lymphopoiesis, which may increase the risk for coronary atherosclerosis.[19] Moreover, E5 suppresses p21 protein expression, a major tumor suppressor, and is reported to curb cellular apoptosis by inhibiting Fas ligand and tumor necrosis factor-related apoptosis-inducing ligand.[20] It is through these mechanisms that HPV can affect multiple components, such as lipid metabolism, apoptosis, inflammation, and endothelial cell function, thereby increasing the likelihood of atherosclerosis.

Human papillomavirus infection has been suggested to occur in the placenta and the breast, which lends credibility to the suggestion that HPV genes may be expressed by vascular or endothelial cells, potentially triggering or enhancing vascular damage and local inflammation.[21,22] In order to contribute to atheroma formation within the coronary arteries, transportation of HPV would need to have occurred. Although the exact mechanism is not well understood, one mechanism involves the idea that HPV-infected cells release extracellular vesicles carrying nucleic acids and proteins.[5] These vesicles may then deliver their contents to cells in arterial walls via the blood stream. Peripheral blood leukocytes have also been suggested to carry HPV nucleic acids and proteins and may provide an alternative route to reach the arterial walls.[23]

Lawson et al[7] showed the presence of high-risk HPV DNA in 55% of atheromatous coronary arteries collected from 20 patients deceased due to myocardial infarction. The expression of E6 and E7 oncoproteins was found in arterial smooth muscle cells, plasma cells, foam cells, and macrophages in atheromatous plaques, which may indicate a direct influence of HPV on the structure of the arterial wall.[7] Arterial stiffness reflects very early alterations of structural (amount and structure of elastin and collagen fibers and other extracellular matrix components) and functional properties of arteries (modulation of vascular tone by contraction and relaxation of medial smooth muscle cells), and is considered to be an independent marker of cardiovascular risk. Increased arterial stiffness leads to vessel damage and, ultimately, atherosclerosis. This, in turn, results in an evidently heightened risk for atheroma formation. As such, although there is sparse current literature describing this relationship, HPV's potential effect on arterial stiffness and subsequent hypertension may be one of the pathophysiologic mechanisms contributing to an increased risk of cardiovascular disease.

Human Papillomavirus and Diabetes Mellitus

The interaction between HPV and diabetes mellitus has not been well established in the literature. However, diabetic patients have been shown to have altered T cell and macrophage proliferation, impaired natural killer cell and B cell function, and therefore, have an abnormal innate and adaptive immunity.[24] As such, it is reasonable to deduce that diabetic patients are likely at an increased risk of HPV infection. To support, Yue et al[25] showed that in high-risk HPV-infected patients who had high-grade squamous intraepithelial lesion there was an association with diabetes and prediabetes with cervical cancer.

As previously explained, HPV can induce systemic inflammation by up-regulating pro-inflammatory cytokines. In doing so, HPV infections in diabetic patients may persist, or even recur, as the combination of a worsened immune system and inflammatory setting leads to an environment that may be less capable of clearing infection. This process can then potentially activate a vicious cycle whereby HPV infections become more clinically significant the longer they persist, given its pathogenetic mechanisms in diabetic patients.

Human Papillomavirus and Hyperlipidemia

Acute infections have been shown to alter plasma lipid levels.[26] Particularly, total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) levels are decreased and plasma triglyceride

levels are elevated or inappropriately normal for patients with poor nutritional status.[26] Despite LDL-C levels decreasing, the concentration of small dense LDL has been found to be increased during infections. These changes have also been shown to positively correlate with the severity of the infection, whereby a more severe infection will result in more significant alterations.[26] Accordingly, in the acute setting of an HPV infection, a lipid profile resembling these anticipated changes may be expected.

Furthermore, epidemiologic studies have suggested that low cholesterol, LDL-C, and HDL levels increase the chance of developing an infection.[26] Through this link, a cycle may then begin to take place that ultimately results in a potentially persistent HPV infection. As previously described, HPV has been shown to induce a pro-inflammatory state and therefore, a chronic HPV infection may up-regulate inflammatory cytokines, which will not only enhance the aforementioned lipid changes, but may also increase Lp(a), a nonmodifiable risk factor for cardiovascular disease.[26] In support of these findings, a recent study by Cheng et al[27] on 1589 cervical cancer patients found that patients with cervical cancer had significantly elevated levels of total cholesterol, triglycerides, and LDL-C compared with controls. Regression analysis demonstrated that high total cholesterol, triglycerides, and LDL-C were significant risk factors for cervical cancer.[27] Thus, the pathophysiologic mechanism of chronic HPV infection may result in dyslipidemia and ultimately, an elevated risk for cardiovascular disease.

Human Papillomavirus and Atherosclerosis

The effect of chronic infections, particularly with respect to HPV, on the development, progression, or destabilization of atherosclerotic cardiovascular disease seems to be mediated predominantly by increased pro-inflammatory activity and altered lipid metabolism. Through HPV's ability to up-regulate the nuclear transcription factor NFκB and the cytokines interleukin-6, tumor necrosis factor alpha and interleukin-1B, a chronic inflammatory state results, which may affect various risk factors that have been shown to contribute to atherosclerosis, such as endothelial dysfunction, arterial stiffness, and dyslipidemia. This appears to be one of the processes that link HPV and atherosclerosis.

Human papillomavirus has also been described in the literature as an emerging factor for atypical infection-associated atherosclerosis.[16] Because HPV replicates locally without the development of classical viremia, the acceleration of the process of atherosclerosis is assumed to be related particularly to the effect of chronic local cervical-vaginal inflammation.[6,28] The viral oncoproteins E6

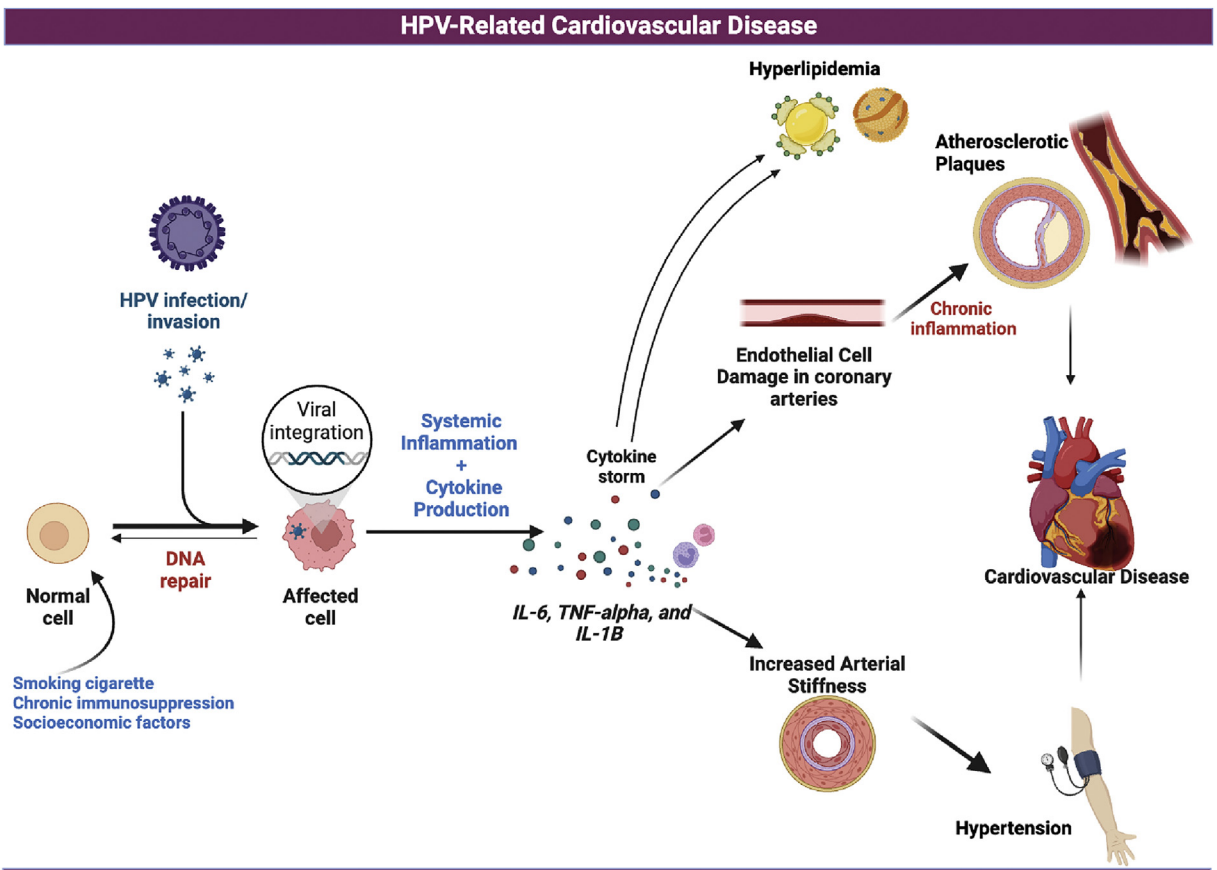

Figure Proposed pathophysiologic relationship between human papillomavirus infection and development of cardiovascular disease.

degrades the tumor-suppressor protein p53, which in addition to the regulation of cell-division, plays a key role in the regulation of atherosclerotic processes.[16] As previously mentioned, a diminished availability of p53 accelerates atherosclerosis, stimulates the formation of atherosclerotic plaques, and inhibits apoptosis of the infected cells.[16] Zekavat et al[17] were able to demonstrate in their study that the p53-deficient macrophage has a selective advantage to expand within the arterial wall, based mechanistically on the fact that p53 deficiency results in increased proliferation, thereby increasing macrophage burden in atherosclerotic plaques and accelerating cell cycle kinetics. Furthermore, HPV oncoproteins stimulate nuclear localization of active caspase-8, an enzyme contributing to the regulation of apoptosis, the inflammatory processes in the vessels, and atherosclerosis itself.[7,29,30] The two aforementioned mechanisms help shed some light onto the manner in which HPV may in fact increase the risk for atherosclerosis.

CONCLUSIONS

There is increasing recognition of the association between HPV infection and risk of cardiovascular disease. However, despite compelling evidence for the association between the two and plausible mechanisms for the development of cardiovascular disease with HPV infection (Figure), a causative relationship has yet to be firmly established. In part 2 of this series, we continue with a discussion of the correlation between HPV and cardiovascular mortality, potential prevention and treatment strategies for HPV-related cardiovascular disease, and the future direction of the research.

References

1. Hall E, Wodi AP, Hamborsky J, Morelli V, Schillie S. *Centers for Disease Control and Prevention. Epidemiology and Prevention of Vaccine-Preventable Diseases*. 14th ed. Washington, DC: Public Health Foundation; 2021.
2. 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.
3. Shanmugasundaram S, You J. Targeting persistent human papillomavirus infection. *Viruses* 2017;9(8):229.
4. Harden ME, Munger K. Human papillomavirus molecular biology. *Mutat Res/Rev. Mutat. Res.* 2017;772:3–12.
5. Reis DRA, Medeiros-Fonseca B, Costa JM, et al. HPV infection as a risk factor for atherosclerosis: a connecting hypothesis. *Med Hypotheses* 2020;144:109979.
6. Kuo HK, Fujise K. Human papillomavirus and cardiovascular disease among US women in the National Health and Nutrition Examination Survey, 2003 to 2006. *J Am Coll Cardiol* 2011;58(19):2001–6.
7. Lawson JS, Glenn WK, Tran DD, Ngan CC, Duflou JA, Whitaker NJ. Identification of human papilloma viruses in atheromatous coronary artery disease. *Front Cardiovasc Med* 2015;2:17.
8. Joo EJ, Chang Y, Kwon MJ, Cho A, Cheong HS, Ryu S. High-risk human papillomavirus infection and the risk of cardiovascular disease in Korean women: a cohort study. *Circ Res* 2019;124(5):747–56.
9. Brito LMO, Brito HO, Corrêa RDGCF, et al. Human papillomavirus and coronary artery disease in climacteric women: is there an association? *Sci World J* 2019;2019(1):1872536.
10. Liang X, Chou OHI, Cheung BM. The effects of human papillomavirus infection and vaccination on cardiovascular diseases, NHANES 2003-2016. *Am J Med* 2023;136(3):294–301.
11. Cheong HS, Chang Y, Kim Y, et al. Human papillomavirus infection and cardiovascular mortality: a cohort study. *Eur Heart J* 2024;45(12):1072–82.
12. Perkins ND. The diverse and complex roles of NF-κB subunits in cancer. *Nat Rev Cancer* 2012;12(2):121–32.
13. James MA, Lee JH, Klingelhutz AJ. Human papillomavirus type 16 E6 activates NF-kappaB, induces cIAP-2 expression, and protects against apoptosis in a PDZ binding motif-dependent manner. *J Virol* 2006;80(11):5301–7.
14. Xu M, Katzenellenbogen RA, Grandori C, Galloway DA. NFX1 plays a role in human papillomavirus type 16 E6 activation of NFkappaB activity. *J Virol* 2010;84(21):11461–9.
15. Ballocca F, D'Ascenzo F, Gili S, Grosso Marra W, Gaita F. Cardiovascular disease in patients with HIV. *Trends Cardiovasc Med* 2017;27(8):558–63.
16. Tonhajzerova I, Olexova LB, Jurko A, et al. Novel biomarkers of early atherosclerotic changes for personalised prevention of cardiovascular disease in cervical cancer and human papillomavirus infection. *Int J Mol Sci* 2019;20(15):3720.
17. Zekavat SM, Viana-Huete V, Matesanz N, et al. *TP53*-mediated clonal hematopoiesis confers increased risk for incident atherosclerotic disease. *Nat Cardiovasc Res* 2023;2(2):144–58.
18. Kim SH, Juhnn YS, Kang S, et al. Human papillomavirus 16 E5 upregulates the expression of vascular endothelial growth factor through the activation of epidermal growth factor receptor, MEK/ERK1,2 and PI3K/Akt. *Cell Mol Life Sci* 2006;63(7-8):930–8.
19. Zhou Y, Zhu X, Cui H, et al. The role of the VEGF family in coronary heart disease. *Front Cardiovasc Med* 2021;8:738325.
20. Bhattacharjee R, Das SS, Biswal SS, et al. Mechanistic role of HPV-associated early proteins in cervical cancer: molecular pathways and targeted therapeutic strategies. *Crit Rev Oncol Hematol* 2022;174:103675.
21. Weyn C, Thomas D, Jani J, et al. Evidence of human papillomavirus in the placenta. *J Infect Dis* 2011;203(3):341–3.
22. De Carolis S, Storci G, Ceccarelli C, et al. HPV DNA associates with breast cancer malignancy and it is transferred to breast cancer stromal cells by extracellular vesicles. *Front Oncol* 2019;9:860.
23. Vergara N, Balanda M, Vidal D, Roldán F, SM H, Ramírez E. Detection and quantitation of human papillomavirus DNA in peripheral blood mononuclear cells from blood donors. *J Med Virol* 2019;91(11):2009–15.
24. Yue C, Zhang C, Ying C, Jiang H. Diabetes associated with HPV infection in women aged over 50 years: a cross-sectional study from China's largest academic woman's hospital. *Front Endocrinol (Lausanne)* 2022;13:972963.
25. Yue C, Zhang C, Ying C, Jiang H. Diabetes associated with cervical carcinoma among high-risk HPV-infected patients with cytologically diagnosed high grade squamous intraepithelial lesion. *Front Endocrinol (Lausanne)* 2022;13:993785.
26. Khovidhunkit W, Kim MS, Memon RA, et al. Effects of infection and inflammation on lipid and lipoprotein metabolism: mechanisms and consequences to the host. *J Lipid Res* 2004;45(7):1169–96.
27. Cheng L, Li Z, Zheng Q, Yao Q. Correlation study of serum lipid levels and lipid metabolism-related genes in cervical cancer. *Front Oncol* 2024;14:1384778.
28. Prétet JL, Mercier M, Riethmuller D, Aubin F, Vuitton D, Mougin C. Human papillomavirus and cardiovascular disease. *J Am Coll Cardiol* 2012;60(1) [81-82; author reply 82-83.
29. Usui F, Shirasuna K, Kimura H, et al. Critical role of caspase-1 in vascular inflammation and development of atherosclerosis in Western diet-fed apolipoprotein E-deficient mice. *Biochem Biophys Res Commun* 2012;425(2):162–8.
30. Manzo-Merino J, Massimi P, Lizano M, Banks L. The human papillomavirus (HPV) E6 oncoproteins promotes nuclear localization of active caspase 8. *Virology* 2014:450–1 [146-152.