

**Human papillomavirus infection and cardiovascular disease:  
A topic of interest for researchers**  
*İnsan papilloma virüsü enfeksiyonu ve kardiyovasküler hastalıklar:  
Araştırmacıların yeni ilgi alanı*

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Infection and inflammation are regularly linked to cardiovascular disease (CVD). Human papilloma virus (HPV) is a common infection, and the focus of this research was an exploration of a potential association between CVD and HPV infection. Laboratory studies have indicated a relationship between HPV infection and atherosclerosis. Clinical surveys have also reported that HPV-infected patients have lipid and blood pressure abnormalities. HPV infection in women appears to increase the incidence of CVD, especially coronary artery disease (CAD). Additional inquiry to determine whether treatment or vaccination against HPV could reduce the prevalence of CVD is needed. The association between HPV and atherosclerosis should be a topic of interest to researchers.

The identification of preventive measures for CVD is a subject of broad research interest. Infection and inflammation are frequently associated with CVD. Many infectious agents have been suggested as the cause of the initial inflammation in atheromatous disease. Women with a genital HPV infection have recently been reported to have a higher incidence of CVD events, including myocardial infarction and stroke.<sup>[1]</sup>

It has been hypothesized that chronic infection may affect the development, progression, and destabilization of atherosclerotic CVD. These pathogens have adverse effects on the endothelium and smooth muscle of the arteries by increasing pro-inflammatory activity and altering the lipid metabolism early in life. Such

mechanisms can act both locally, such as increasing expression of adhesion molecules and oxidation of low-density lipoprotein, or systemically, increasing the release of cytokines stimulating both innate and adaptive immune responses, and increasing the quantity of interleukins or T-helper cells. These factors and many others may work directly or indirectly. The Canakinumab Anti-inflammatory Thrombosis Outcomes Study demonstrated that inhibition of the interleukin pathway of innate immunity led to reduced vascular risk.<sup>[2]</sup>

The mechanisms underpinning this interaction are still a subject of investigation, but progressive atherosclerosis is thought to make a significant contribution.<sup>[1]</sup>

Since HPV replicates locally without the development of classic viremia, the acceleration of the process of atherosclerosis is assumed to be related particularly to the effect of chronic local vaginal inflammation, which causes increased levels of circulating inflammatory mediators. A recent study showed the presence of high-risk HPV DNA in 55% of atheromatous coronary arteries collected from 20 patients who died as a result of myocardial infarction.<sup>[3]</sup> Pro-inflammatory mediators can cause increased intima-media thickness, which can make an atherosclerotic event, endothelial dysfunction, and arterial stiffness more likely. These complex mechanisms promote both atheromatosis and arteriosclerosis.<sup>[2]</sup>

**Abbreviations:**

CAD	Coronary artery disease
CVD	Cardiovascular disease
HPV	Human papilloma virus

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A review of the literature identified only a small number of studies exploring the association between HPV infection and atherosclerotic CVD, however, there are studies that have reported a possible strong association (Table 1).<sup>[4,5]</sup> A clinical association was noted in 2 epidemiological data reports and a genetic analysis. In a cohort of more than 63,000 women followed-up for 5 years, high-risk HPV (7.6%) was shown to have a significant relationship with CVD. The hazard ratio for the incidence of CVD was 1.23 (95% confidence interval: 1.01–1.50). The study was adjusted for other potential contributing factors, such as blood cholesterol and glucose, blood pressure, smoking status, family history of CVD, age, body mass index, alcohol intake, and physical activity.<sup>[4]</sup>

In a cross-sectional study of 2450 women, a vaginal swab was assessed for the presence of HPV DNA. The study revealed that the women who had a prior genital HPV infection had a 2.5- to 3-fold increased incidence of myocardial infarction or stroke compared with HPV-negative women.<sup>[5]</sup> In addition, another study indicated that there was an increased risk of stroke or transient ischemic attack in HPV-positive patients after radiation therapy for head and neck cancer.<sup>[6]</sup> Furthermore, a study found that HPV-positive patients had a lower level of high-density lipoprotein and higher systemic blood pressure.<sup>[7]</sup> A gene sequence study of atheromatous plaques in CAD indicated HPV-positive status in 55%, highlighting the potential role in the occurrence of CAD.<sup>[3]</sup>

The pathophysiological mechanisms are complex and not well understood. HPV, as any other infection, may play an initiating role in atherosclerotic CVD. This is supported by the following observations: Firstly, the triggering process for atheromatous arterial disease is of inflammatory origin.<sup>[1]</sup> HPV infection usually causes a persistent inflammatory reaction. Secondly, the HPV genes E6 and E7 immortalize atheromatous plaque-derived aortic smooth muscle cells. Thirdly, giant cell arteritis of the temporal artery has been associated with HPV infection. HPV DNA has been detected

**Table 1. Summary of available case reports and studies addressing HPV and atherosclerotic CVD in the literature**

Authors	Year	Origin (country)	Type of article	Type of study	Number of study participants	Type of evaluation	Method of HPV detection	Follow-up duration	Major findings
Joo et al.	2019	South Korea	Prospective study	Prospective cohort study	63,411	PAP cervical sample DNA	Cervical sample DNA testing	2011–2016	HPV positivity was significantly associated with the 5-year incidence of CVD, and the hazard ratio for the incidence of CVD in high-risk-HPV-positive women was 1.23 (95% confidence interval 1.01–1.50) compared with high-risk-HPV-negative women
Lawson	2015	USA	Case report	Case control	20	Post mortem	Polymerase Chain Reaction techniques were used to identify HPV gene sequences. Immunohistochemistry	–	HPV gene sequences were identified in 55% of atheromatous coronary arteries
Kuo and Fujise	2011	USA	Survey	Population-based cross-sectional study	2450	Self-reported data of CVD and self-collected vaginal swabs	HPV-DNA	2003–2006	2.5-fold increased incidence of severe cardiovascular complications (myocardial infarction, stroke)

CVD: Cardiovascular disease; HPV: Human papilloma virus.

in biopsy samples of the temporal arteries of patients diagnosed with giant cell arteritis, and HPV type 16 in the endothelial cells of neurons and vessels of cervical cancer patients.<sup>[4,8]</sup>

Research to test the hypothesis that HPV infection may promote atheroma formation in infected patients suggested that the infection may promote systemic inflammation or affect blood vessels directly through the nucleic acids contained in extracellular vesicles, such as exosomes.<sup>[9]</sup>

Both caspases and oncoprotein enzymes are modulated by E5 and E6 proteins of HPV type 16, which affect the membrane lipids in keratinocytes that influence apoptosis and contribute to vascular inflammation and the development of atherosclerosis. The E6 and E7 oncoproteins have been found in atherosclerotic plaques in macrophages, foam cells, plasma cells, and arterial smooth muscle cells.<sup>[3]</sup> It has also been noted that HPV with E6 and E7 oncoproteins was transferred to atherosclerotic plaques through the monocytes and macrophages implanted in HPV infected tissues.<sup>[8]</sup>

In patients with nasopharyngeal carcinoma, bioinformatics analysis of differentially expressed genes that explained molecular mechanisms led to the identification of putative targets. The results of the Kyoto Encyclopedia of Genes and Genomes pathway analysis indicate that upregulated differentially expressed genes were linked to several pathways, including HPV.<sup>[10]</sup>

Antibiotics and viral vaccines are known to reduce atheroma in animals.<sup>[11]</sup> Treating or vaccinating women with HPV might affect the prevalence of CVD if this relationship can be firmly established. Additional research is required to confirm the applicability of these processes in humans.

Antivirals and antibiotics have not been successful in clinical trials examining atherosclerotic CVD. One possible reason is that most studies are conducted with patients who have severe atherosclerotic CVD. Use as a tool of primary prevention with the HPV vaccine offered to young girls and women could be beneficial.

In conclusion, HPV infection in women appears to increase the incidence of CVD, especially CAD.

Additional investigation is required to determine whether treatment or vaccination for HPV would reduce the prevalence of CVD. HPV and atherosclerosis is a topic that should be of interest to researchers.

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