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EDITORIAL
Epidemiology, prevention, and health care policies

Human papilloma virus and atherosclerotic cardiovascular disease

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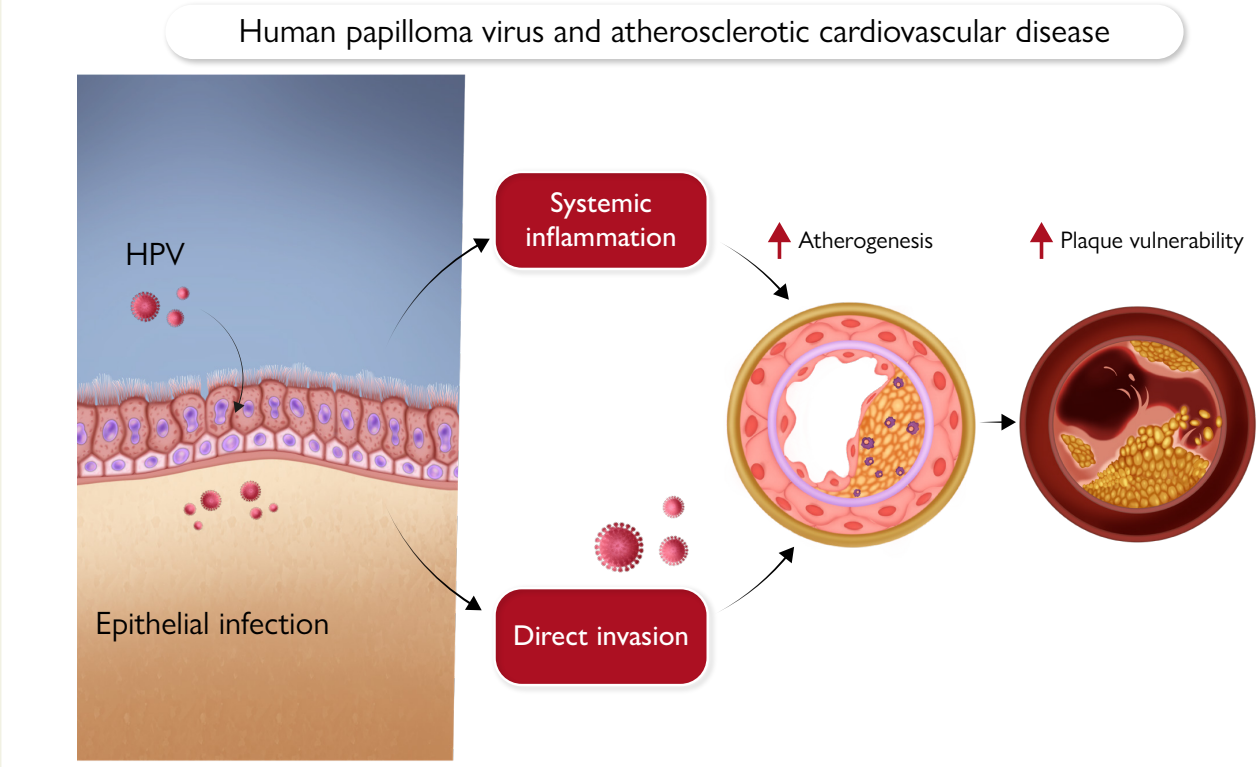
This editorial refers to 'Human papillomavirus infection and cardiovascular mortality: a cohort study', by H.S. Cheong *et al.*, https://doi.org/10.1093/eurheartj/ehae020.

Graphical Abstract



Human Papilloma virus (HPV) is a non-enveloped DNA virus that infects cervical epithelial cells and is a known cause of cervical cancer in women. Less known are the findings of recent epidemiological studies that associate HPV with a higher risk of atherosclerotic cardiovascular morbidity and mortality. There are at least two possible ways in which HPV infection can contribute to this process and its complications. First, HPV could directly invade atherosclerotic plaques, thereby causing plaque progression and/or instability. Although the prevailing opinion is that HPV is an infection limited to epithelial cells, some authors have reported the detection of HPV DNA and protein in atheromatous coronary arteries as well as in endothelial cells, smooth muscle cells, plasma cells and foamy macrophages located in these plaques. The transport mechanism to infect distant sites is still being elucidated but a possibility is that extra-cellular vesicles, which contain HPV DNA released from infected cells, transport the viral elements in blood to other sites. Second, HPV infection could trigger a systemic inflammatory response (including inflammasome activation) that accentuates atherosclerosis and promotes plaque instability.

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In contemporary practice, the pillars of prevention and treatment of atherosclerotic cardiovascular disease (ASCVD) comprise behavioural changes (smoking cessation, exercise, and healthy eating), screening and modification of conventional risk factors (lipid, glucose, and blood pressure-lowering therapies), and antithrombotic therapy. Despite advances in screening for conventional risk factors and their treatment, ASCVD remains a leading cause of morbidity and mortality worldwide (accounting for one-third of global deaths). Consequently, it is probable that there are other causal risk factors that are yet to be discovered or accepted by mainstream medicine.

For decades, infectious agents have been proposed to be potential risk factors for atherosclerosis. Studies in experimental animal models have reported that infection with pathogenic organisms, including cytomegalovirus,[1] human immunodeficiency virus (HIV),[2] *Porphyromonas gingivalis*,[3] and *Chlamydia pneumoniae*,[4] induces atherosclerosis, a process which is accelerated by high-fat diets.

Human clinical studies investigating these same pathogens have also reported an association between infections and atherosclerosis.[1,3–5] However, because of the lack of high-quality evidence, infection as a causal risk factor for atherothrombosis has not gained traction.

Interest in a causal role for viral infections in the pathogenesis of atherosclerosis and its complications has been rekindled by several recent publications. In this issue of the *European Heart Journal*, Cheong and colleagues report a large cohort study that has provided robust evidence that viruses contribute to the clinical burden of atherosclerosis.[6] In a prospective cohort of 163 250 Korean women with no known ASCVD who have been tested for high risk for cancer human papilloma virus (HR-HPV) infection and followed up for 17 years (median 8.6 years), Cheong and colleagues examined the association between HR-HPV infection and cardiovascular (CVD) disease mortality. At baseline, the women had a mean age of 40.4 years, and a low prevalence of conventional risk factors (smoker < 4.7%, hypertension < 6.8%, diabetes < 2.3%, use of lipid-lowering therapy < 2.6%). Of these women, 15 047 (9.2%) were HR-HPV positive. During follow-up, there were a total of 134 cardiovascular deaths, of which 21 (16%) occurred in women with HR-HPV infection.

The associations reported by Cheong *et al*. between HR-HPV infection and adverse cardiovascular outcomes were strong for ASCVD mortality [hazard ratio (HR) 3.91; 95% confidence interval (CI) 1.85–8.26), ischaemic heart disease mortality (HR 3.74; 95% CI 1.53–9.14), and stroke mortality (HR 5.86; 95% CI .86–40.11), respectively. Even after adjusting for CVD risk factors and other possible confounders, the associations remained significant for ASCVD and ischaemic heart disease mortality. Obesity was a risk modifier, magnifying the adverse associations between HR-HPV infection and cardiovascular mortality (HR 4.81 vs. 2.81; *P* for interaction = .006).

The main strengths of the study are its large sample size, the prospective design with 1 380 953 person-years of follow-up, the comprehensive collection of baseline characteristics to enable statistical adjustments for confounders, the almost complete mortality data from the Korea National Statistical Office, where all deaths must be reported, and the multiple analyses that showed consistency of the association across subtypes of cardiovascular mortality. Some limitations include the potential for mis-ascertainment of the cause of death based on ICD-10 coding, the small number of cardiovascular deaths in women with HR-HPV infection, which reduced the robustness of the estimates, and the uncertain generalizability to a non-Asian population (where the prevalence of HPV infection, cardiovascular risk factors, and HPV vaccination may differ). Nonetheless the results are likely to be valid. They extend the findings of smaller studies that have previously associated HPV infection with a higher risk of non-fatal cardiovascular events.[7,8]

Other studies have reported that several viruses are linked to higher cardiovascular morbidity and mortality, including chronic hepatitis B, chronic hepatitis C, HIV, coronavirus disease 2019 (COVID-19), and influenza. The association with influenza stands out because evidence from randomized trials indicates that influenza vaccination prevents major cardiovascular events. In a double blinded randomized trial that compared inactivated influenza vaccine with placebo in 2532 patients after myocardial infarction, vaccination reduced cardiovascular deaths by 41%.[9] Although similar evidence from randomized trials is not available for HPV, a recent stratified analysis by HPV vaccination status in a cross-sectional study that included 9353 women (of whom 40.8% were HPV DNA positive) in the National Health and Nutrition Examination Survey (NHANES 2003–2016) reported a significant adverse association between HPV and cardiovascular disease [odds ratio (OR) = 1.54; 95% CI 1.15–2.08] in unvaccinated women but no adverse association in (OR = .50; 95% CI .07–3.51) in vaccinated women, suggestive of a protection from HPV vaccination.[10]

It is now generally accepted that atherosclerosis is a lipid-driven chronic inflammatory disease, and if so there are several possible ways in which viral infections can accentuate this process and increase the risk of myocardial infarction and stroke (*Graphical Abstract*). First, viruses could directly invade atherosclerotic plaques, thereby causing plaque progression and/or instability. Second, they could trigger a systemic inflammatory response and produce acute prothrombotic changes by activating platelets or the blood coagulability.

Several lines of evidence indicate that viruses can enter and interact with atherosclerotic plaques. In 2015, Lawson *et al*. identified HR-HPV types 16 and 18 in 55% of coronary artery atheromatous plaques and smooth muscle cells in 20 deceased donors, and showed that HPV E7 protein was expressed in smooth muscle cells, plasma cells, foam cells, and macrophages.[11] More recently, Eberhardt and colleagues identified replicating severe acute respiratory syndrome-coronavirus 2 (SARS-CoV2) in coronary atherosclerotic lesions taken at autopsy of patients who died from severe COVID, findings that indicate that SARS-CoV2 can infect coronary vessels and induce plaque inflammation.[12]

The evidence that viruses in general and HPV in particular increase the risk of adverse outcomes from ASCVD has become compelling enough to add to the already strong case for vaccination against influenza virus, SARS-CoV-2, and HPV. The evidence that HPV is causal in the initiation or progression of ASCVD is highly suggestive but would become definitive if the results of randomized trials evaluating HPV vaccines for prevention of cervical cancer showed a reduction in ASCVD.

In summary, the findings of Cheong and colleagues show that HR-HPV infection in Korean women without known ASCVD and with a low prevalence of conventional cardiovascular risk factors is associated with higher cardiovascular mortality. These findings, when added to other evidence linking HPV and other viruses to higher CVD mortality, make a strong case for accepting viruses as risk factors for adverse outcomes from ASCVD.

Declarations

Disclosure of Interest

All authors declare no disclosure of interest for this contribution.

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