Persistent high-risk HPV infection

High viral load

Integrated high-risk HPV DNA

Upregulation of E6 and E7 oncoproteins

**High-risk HPV E6 oncoprotein:**
- induces degradation of P53 tumour suppressor gene
- mediates degradation of the cellular PDZ domain
- induces activation of telomerase

**High-risk HPV E7 oncoprotein:**
- inactivates Rb apoptosis / tumour suppressor gene
- induces chromosome duplication errors
- dysregulates cell cycle through interaction with AP-1 transcription complex, and with CDK inhibitors, p21 and p27
- downregulates expression of MHC Cl.I molecules contributing to HPV persistence

**Genomic Instability**

Modulation of cellular genes

Modulation of viral genes

Environmental and dietary mutagenic factors; tobacco; co-infection with other sexually transmitted agents; oestrogen therapy

**Host immune fitness**

**Viral genetic factors**

**Host and viral epigenetic factors**

**HPV-associated squamous cell carcinoma**

Flow-diagram of high-risk HPV-mediated pathogenesis of squamous cell carcinoma