PRIMEVIEW

CARCINOGENIC HPV INFECTION

nature REVIEWS DISEASE PRIMERS

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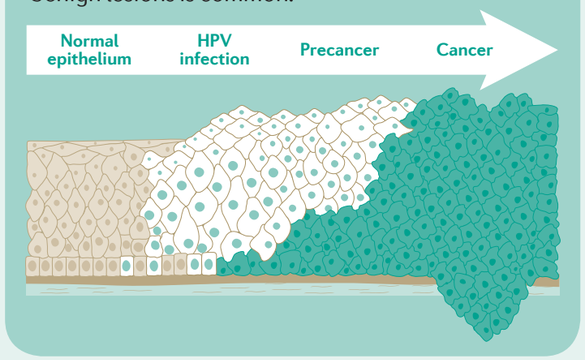
Of the >200 known human papillomavirus (HPV) genotypes, 13 are deemed high risk and associated with human diseases — notably, cervical, vaginal, vulvar, penile, anal and oropharyngeal cancers. These high-risk types belong to the Alpha genus of HPV.

MECHANISMS

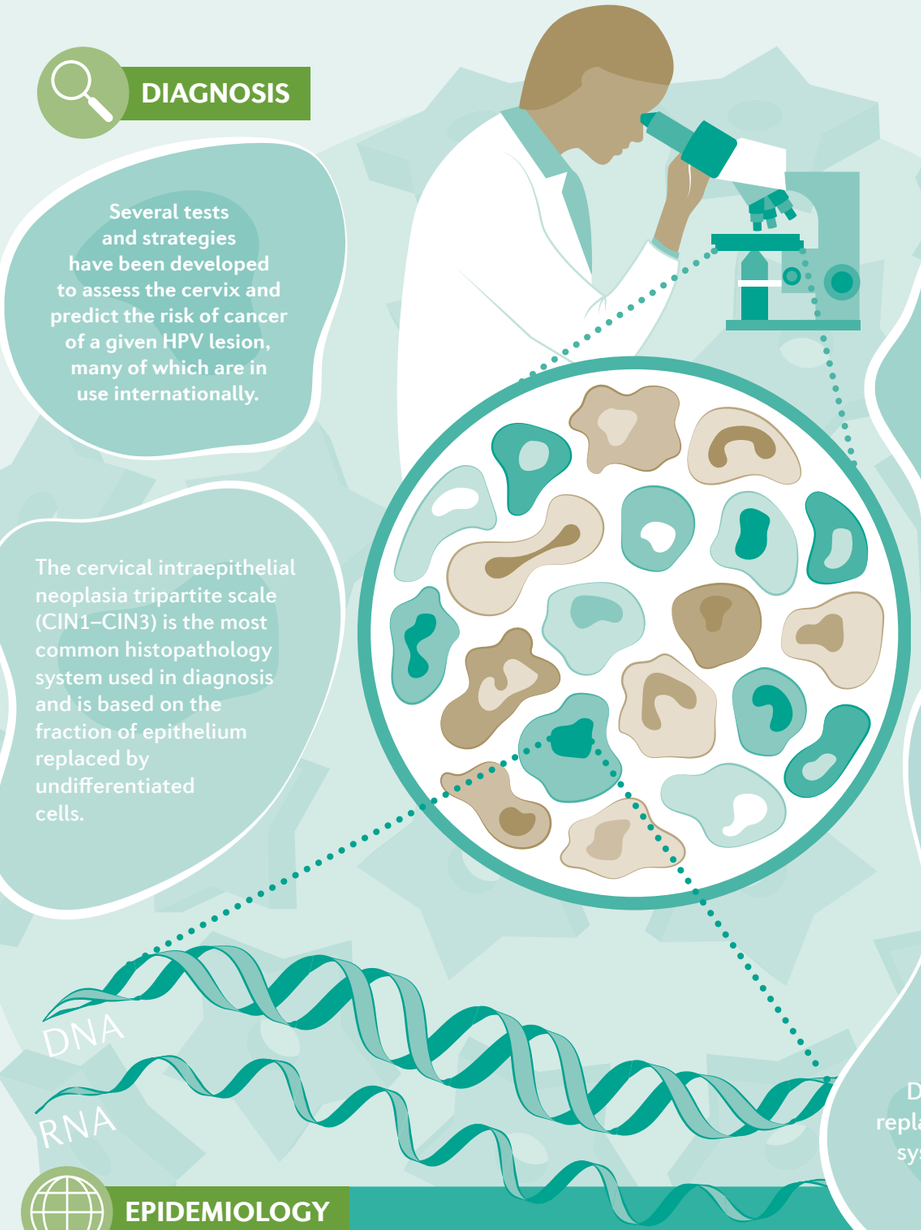
HPV infections are common and primarily transmitted by sexual contact. The virus mainly infects epithelial and mucosal tissues and regulates gene expression as the infected basal cell migrates towards the epithelial surface. The carcinogenicity of HPVs results predominantly from the activity of the oncoproteins E6 and E7, which are viral proteins that impair growth regulatory pathways in the host cell. E6 and E7 expression increase as an infection transitions from a productive (virion-producing) to an abortive (transforming) state, after which cancer can result following the accumulation of host genetic mutations over many years. Most infections (even those of high-risk Alpha HPVs) are controlled immunologically and cleared by the host, such that viral DNA or RNA is undetectable within 2 years. However, which infectious precancerous lesions can be immunologically cleared and which progress cannot be accurately predicted. Although many systems and nomenclatures have been devised to characterize precancerous lesions with the aim of guiding treatment, overtreatment of potentially benign lesions is common.



DIAGNOSIS

Several tests and strategies have been developed to assess the cervix and predict the risk of cancer of a given HPV lesion, many of which are in use internationally.

The cervical intraepithelial neoplasia tripartite scale (CIN1–CIN3) is the most common histopathology system used in diagnosis and is based on the fraction of epithelium replaced by undifferentiated cells.



The Papanicolaou ('Pap') cytology screen is widely used, but HPV DNA testing is being incorporated (or even recommended to replace cytology as the screen) into the technique.

A clinically more-meaningful approach would be tissue classification according to HPV status: normal (no HPV detected), precancer (a lesion with a very high probability of invasion if untreated) or cancer. The cost of implementing HPV, DNA or RNA testing (and replacing current pathology systems) is potentially controversial.

EPIDEMIOLOGY

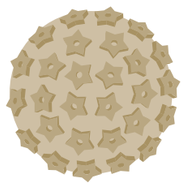
Cervical cancer is the most common HPV-related cancer, with >500,000 cases reported in 2012. Indeed, the fraction of HPV-induced cancers in men is much lower (<1%) than in women (8.6%) because of the unique vulnerability of the cervix. However, the rates of cervical cancer vary greatly between geographical regions owing to the combined effect of prevalence of cervical HPV infection and quality of cervical cancer screening programmes in different countries.

PREVENTION

Three vaccines are currently available that provide coverage against several high-risk HPVs: a bivalent vaccine that offers protection from HPV16 and HPV18, which are responsible for most HPV cancers; a tetravalent vaccine, which provides coverage against HPV16, HPV18, HPV6 and HPV11 (HPV6 and HPV11 commonly cause genital warts); and a nonavalent vaccine that provides protection against HPV16, HPV18, HPV6, HPV11, HPV31, HPV33, HPV45, HPV52 and HPV58. In countries that have implemented a vaccination programme with >50% coverage of adolescent girls, herd protection against genital HPV infections and warts has been later shown in heterosexual women and men.

MANAGEMENT

Cervical precancers are typically excised or ablated. Anogenital cancers are preferentially treated with radical local excision (for example, hysterectomy for cervical cancer) and, when the risk of spread to the lymph nodes is high, with regional lymphadenectomy. For early-stage anogenital cancers, radiotherapy is an acceptable primary therapy; platinum-based chemotherapy can also be given. However, in advanced-stage, metastatic cancer, treatment outcomes are universally poor and focus shifts to palliation.



Currently, HPV status of the tumour does not influence treatment strategy for any HPV-related anogenital cancer

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