Click this link to go to the web page:
http://www.who.int/vaccine_research/diseases/viral_cancers/en/index3.html

Human papillomavirus

- Disease Burden
- Virology
- Vaccines
- Useful Links
- WHO Media Fact Sheet - Development of New Vaccines
- WHO Bulletin - Vaccinating against cervical cancer
- Human Papillomavirus and HPV vaccines - Technical information for policy-makers and health professionals [pdf 1.09mb]

Viral Cancers

1. Introduction
2. Epstein-Barr virus
3. Hepatitis C Virus
4. Human papillomavirus

Disease Burden

Human papillomavirus (HPV) causes cervical cancer, the second biggest cause of female cancer mortality worldwide. Estimates of the number of cervical cancer deaths are around 250,000 per year. The prevalence of genital HPV infection in the world is around 440 million. There are over 100 genotypes of HPV, 40 of which infect human mucosal areas of the upper digestive tract and the ano-genital tract. These are grouped into "high-risk" and "low-risk" types according to the degree of risk of development of cancer after infection with each genotype. Genital HPV infection is extremely common and most often causes no symptoms. A proportion of individuals infected with low-risk HPV types such as HPV-6 or HPV-11 will develop genital warts, whereas a subset of women with high-risk HPVs such as HPV-16 or HPV-18 will develop preneoplastic lesions of cervical intraepithelial neoplasia (CIN). Low-grade cervical dysplasias are common and most regress spontaneously. In contrast, the minority of lesions that progress to high-grade dysplasias tend to persist and/or progress to carcinomas in situ before becoming invasive cancers. The majority of adenocarcinomas of the cervix and of squamous cell cancers (SCC) of the vulva, vagina, penis and anus are caused by HPV-16 and HPV-18 (together accounting for about 70% of cases globally), the remaining 30% being due to other high-risk HPV types (such as HPV-31, -33, -35, -39, -45,-51, -66). The relative importance of different high-risk types varies between countries and regions, but type 16 has the greatest contribution to cervical cancer in all regions. HPV is also associated with other cancers of the anus, head and neck, and rarely, recurrent respiratory papillomatosis in children.

About 500 000 cases of cervical cancer are estimated to occur each year, over 80% of which occur in developing countries, where neither population-based routine screening (eg Papanicolau smear test) nor optimal treatment is available. The highest estimated incidence rates of cervical cancer occur in Africa, Central and South America and Asia.

Epidemiological studies in the USA have reported that 75% of the 15–50 year-old population is infected with genital HPV over their lifetime, 60% with transient infection, 10% with persistent infection (confirmed by detection of HPV DNA in genital samples), 4% with mild cytological signs, and 1% with clinical lesions.

Virology

HPV belongs to the family Papovaviridae. These are small nonenveloped icosahedral viruses with an 8 kbp-long double-stranded circular DNA genome. The papillomavirus genome comprises early and late genes that encode early proteins E1–E7 and late proteins L1–L2. The early proteins are nonstructural proteins involved in replication and transcription of the genome (E1–E5) or in host cell tumoral transformation (E6 and E7), whereas L1 and L2 are the structural capsid proteins of the virion. The low-grade cervical dysplasias correspond to productively infected cells that actively shed virus, whereas high-grade dysplasias and cancers do not produce virions: viral gene expression in these cells is limited to the E6 and E7 oncogenes that are transcribed from randomly integrated viral DNA. The E7 protein is thought to induce cell proliferation and disrupt the cell cycle regulation by inactivation of the Rb family proteins, whereas E6 blocks cell apoptosis by directing the p53 tumor suppressor protein to the proteasome.

continued next page

Vaccines

Prophylactic HPV vaccine candidates are based on recombinant capsid protein L1 and aim to elicit neutralizing antiviral antibodies to protect against infection, while therapeutic vaccine candidates are based on viral oncogenic proteins E6 and E7, with or without L1, and aim to induce cell-mediated immune responses to eliminate the transformed tumor cells.

The most advanced and promising approach for a prophylactic vaccine involves the use of noninfectious recombinant virus-like particles (VLPs) which self-assemble spontaneously from pentamers of the L1 capsid protein. These VLPs can be produced in baculovirus-infected insect cells, in yeast, or in other cell substrates. They induce high titres of virus-neutralizing antibodies even in the absence of an adjuvant. In preclinical studies, vaccination of animals resulted in excellent protection from homologous virus challenge, and passive transfer of antibodies from the vaccinated animals also conferred protection,confirming the importance of neutralizing antibodies.

Two prophylactic vaccine candidates are at the level of Phase III clinical evaluation and the companies have filed for licensure. GSK is focusing on a bivalent HPV-16,-18 VLP vaccine candidate and Merck is developing a tetravalent vaccine based on VLPs from HPV-6, -11, -16, and -18. Both showed very high efficacy in proof-of-principle studies and the manufacturer have announced results showing almost 100% protection against high-grade cervical cancer precursors caused by HPV types 16 and 18 in women aged 16-25 years. Other candidate prophylactic HPV vaccines are in development and entering clinical trials.

A number of therapeutic vaccine candidates also have been developed, several of which have undergone Phase I/II clinical evaluation.

Useful Links

- WHO Department of Reproductive Health and Research
- WHO Cancer homepage
- International Agency for Research on Cancer (IARC) [new window]
- Alliance for Cervical Cancer Prevention [new window]
- Child and Adolescent Health and Development
- Programme for Appropriate Technology in Health
- Institut Catalan de Oncologia
- WHO HPV LabNet Page

Viral Cancers: 1,2,3,4