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Human papilloma virus (HPV) associated cancers represents a special subgroup of cancers which are potential targets of screening strategy to reduce the burden of HPV-associated cancers. The viruses have different molecular pathways which ultimately lead to the immortalization of cells. The unique pathobiology and detailed discovery of molecular signaling pathways have paved the new dimensions and advancements in both early detection and development of newer treatment strategy in terms sensitivity towards radiotherapy in HPV-induced cancers versus others. Their clinical behavior suggests good prognosis when compared to Non-HPV positive group cancers. The better prognosis between HPV positive and Non-HPV positive cancer demands a timely diagnosis of HPV status to stratify high risk cases to promote personalized management.

Keywords: HPV, pathology of cancers.

Impact of HPV on the Pathobiology of Cancers
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Abstract

Human papilloma virus (HPV) associated cancers represents a special subgroup of cancers which are potential targets of screening strategy to reduce the burden of HPV-associated cancers. The viruses have different molecular pathways which ultimately lead to the immortalization of cells. The unique pathobiology and detailed discovery of molecular signaling pathways have paved the new dimensions and advancements in both early detection and development of newer treatment strategy in terms sensitivity towards radiotherapy in HPV-induced cancers versus others. Their clinical behavior suggests good prognosis when compared to Non-HPV positive group cancers. The better prognosis between HPV positive and Non-HPV positive cancer demands a timely diagnosis of HPV status to stratify high risk cases to promote personalized management.

Keywords: HPV, pathology of cancers.

Impact of HPV in promoting Neoplasia

Apart from affecting human beings, the infection of HPV has also reported in snakes, birds and tortoises. A huge number of approximately 170 types of HPVs which have been completely sequenced and there are further 200 more are under process. HPV 16 belongs to the family Papillomavirida is a non–enveloped virus which is icosahedral shaped double stranded circular DNA virus. The size of this virus is only 55nm [Figure 1]. Six proteins which are namely (E1, E2, E4, E5, E6, E7) are expressed early while two late proteins (L1 and L2) are expressed later then early proteins in HPV life cycle.

The early proteins have their specific function in overall pathobiology which promotes the immortalization of cell.

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Viral DNA replication is supported by E1 and E2. Post transcriptional modification of virus is being guided by E4. E5 promotes upgradation of growth factor receptors and transformation of cell. The Ubiquitin mediated degradation of tumor suppressor protein (p53) which ultimately make the cell resistant to apoptosis is done by E6. Degradation of retinoblastoma protein (Rb) promoted by E7 binds leading downstream signaling of E2F factor promoting uncontrolled cell division by early entry of cell to synthesis phase (S-phase). The simultaneous action of both E6/E7 oncoprotein together results in immortalization of the virus infected cell.

The viral capsid formation is done by L1 major protein and L2 promotes the entry of viral DNA to genome of host cell.

Once, the host cell is infected by virus it leads to increased expression of all early and late viral proteins by progressive cell divisions. This results in degradation of host tumor suppressor protein such as p53 and Rb. This infected cell continues to remain in prolonged cell cycle with failure of apoptotic mechanism. Finally, it results in unstable genome and immortalization.

The Surrogate Marker of HPV: P16 Expression

The p16 protein expression in tumor act as surrogate marker for HPV. The p16 protein inhibits Rb protein phosphorylation which is mediated by CDK4 and cyclinD1. Hence the expression of p16 increases when Rb is degraded by HPV E7 oncoprotein as a result of feedback loop mechanism.

Cancer Screening: A Molecular Diagnostics approach

The involvement of HPV in cancer other than cervical cancer has broadened its horizon to other tumors. HPV is also involved in specific group of head and neck cancer, oropharyngeal, anal canal, vulvo–vaginal cancers. This may be as a result altered sex habits and co–infection/prior infection of other viruses. Though, different site of tumors, molecular patho–biology and persistent neoplastic insults appears to be similar in all tumors. There has been drastic improvement in diagnostic technique which has significantly contributed in improving the sensitivity of HPV detection rates.

The diagnostics of HPV for cancer screening has been classified on their basic techniques utilized or target amplification. The DNA based methods includes polymeric chain reaction (PCR) mostly utilizing L1 region primer for amplification. The Hybrid Capture II (HC2; Qiagen, Gaitherberg, MD) is the first of all FDA–approved test for screening of High–Risk HPV DNA. This Test uses Hybrid Capture II technology as a nucleic acid hybridization assay with signal amplification that utilizes microplate chemiluminescent detection. The next generation test has come up which are based on mRNA ie, Aptima which can detect mRNA of 12 high risk HPV virus. Many of the studies have been done, which declares this test as equally sensitive but more specific for HPV detection when compared with DNA based HC–II test.

Cancer Cervix

HPV is the single most important causative agent in cancer of cervix, accounting for more than 95% of cases. In an Indian population–based study, the high–risk HPV (hr HPV) was found in 87.8% of squamous cell carcinomas (SCC) of cervix. The HPV infection initially causes in CIN1 (Cervix Intraepithelial Neoplasia–1), which in most of the cases undergoes spontaneous regression. However, in patients with HPV16 or 18 infections or with a high viral load, the CIN might persist for a longer duration and eventually progress to CIN2/3. HPV16 viral loads are a stronger predictor for the persistence of lesions than other strains. Wang et al. evaluated the prognostic value of HPV genotypes in 327 cervical cancer patients who underwent treatment with radiotherapy alone or concurrent chemo–radiation.22 different genotypes of HPV were detected in 98.8% patients and the most common genotypes were HPV 16, 58, 18, and 33. There was a significant improvement in response and cure rates in patients with HPV 18 and HPV 58 positive tumors receiving chemoradiotherapy.
Vulvovaginal Cancer

Vulvovaginal cancers are also associated with HPV, though the degree of association is not as strong as that in cancer cervix. HPV is associated with 70% of vaginal cancers and 43% of vulvar cancers. An increase in the incidence of vulvar cancers reported mainly in younger women has been attributed to HPV and mechanisms similar to those of cervical cancer development have been documented. The role of HPV–related vaccine seems encouraging and the studies have shown a significant reduction of HPV–related anogenital diseases in young females.[21]

Anal Cancer

The association of HPV in the development of anal cancers is well–documented in literature. HPV is associated with 88% of anal cancers. There is an increase in the incidence of anal cancer over the last few decades mainly attributed in homosexual men and Human immunodeficiency virus (HIV) positive groups.[22] There is emerging evidence that anal intra epithelial neoplasia (AIN) is a precursor of anal cancer and unlike cervical cancer, the evidence is mainly from small studies with a follow–up duration of only 5–10 years.[23]

Head and Neck Cancer

HPV is recognized as an independent cause of oropharyngeal cancer. Sixty–three percent of oropharyngeal cancers each year are associated with HPV infection.[2] Base of the tongue and the tonsils are the common primary site with HPV–associated oropharyngeal cancers.[23] Hong et al showed that patients with HPV–positive cancers had a better outcome when treated with radical radiotherapy ± chemotherapy or surgery and adjuvant radiation.[24] Sathish et al. showed that HPV oropharyngeal cancer have a higher likelihood of a complete response to treatment.[25] HPV associated cancers have favorable treatment outcomes and thus generate a hypothesis of de–escalation in these tumors to decrease long term treatment related toxicities.

Cancer Penis

HPV is associated with cancer Penis in 50% of cases. As cancer penis is very rare, there is a paucity of literature. However, HPV 16 is the most common subtype.[26]

Conclusions

HPV associated cancers represents a special subgroup of cancers. HPV integrate with the host tissue and causes carcinogenesis in a phased manner. With vaccination, the incidence of HPV associated cancers can be decreased. With the use of different HPV based screening tests, they can be detected early. Overall, HPV associated cancers have a good prognosis as compared to the non–HPV subtype and there is a growing thought on treatment de–escalation in these tumors to decrease long term treatment related toxicities.

References


