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Overview

The Human Papillomavirus as a Common Pathogen in Oropharyngeal, Anal and Cervical Cancers

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Abstract

The burden of human papillomavirus (HPV)-related cancers worldwide is significant. Although the incidence of cervical cancer is decreasing due to cervical screening programmes, the incidences of oropharyngeal, anal and vulval cancers are increasing. The introduction of HPV vaccination programmes in many countries has had an impact on HPV infection rates but due to the time-lag from initial HPV infection to the development of invasive carcinoma, the impact on the incidence of HPV-related cancer will take more time to become evident. This review explores the common aspects of HPV-related cancers and how they differ from their HPV-negative counterparts, both clinically and molecularly. It also covers the implications this has on future treatment strategies, including the possible role of immunotherapy.

Key words: Anal cancer; cervical cancer; human papillomavirus; oropharyngeal cancer

Statement of Search Strategies Used and Sources of Information

PubMed was searched for publications published in English with the terms 'human papillomavirus' OR 'cervical cancer' OR 'oropharyngeal cancer' OR 'anal cancer' OR 'vulval cancer' OR 'human papillomavirus vaccination' OR 'cervical intra-epithelial neoplasia' OR 'anal intra-epithelial neoplasia' OR 'immunotherapy'. Articles that met these criteria and were available on PubMed before 8 January 2018 were included. In addition, the ClinicalTrials.gov database was searched for studies that included the terms 'human papillomavirus' and 'vaccination' or 'immunotherapy'.

Introduction

Human papillomaviruses (HPV) are double-stranded DNA viruses that can cause both benign diseases, precancerous lesions and invasive malignancy. There are over 170 types [1], with 12 currently classified as carcinogenic [2]. HPV-16, -18, -31, -33, -35, -41, -52 and -58 are the most important globally [3]. HPV infects the basal keratinocytes of genital mucosa, oral mucosa and skin and is predominantly spread by sexual contact. Ninety-one per cent of individuals infected with HPV will clear the infection within 2 years [4]. Persistent infection is necessary for carcinogenesis.

The HPV genome consists of six early genes (E1, E2, E4, E5, E6 and E7) and two late genes (L1 and L2) [5]. In benign lesions, the HPV genome usually remains episomal, but for cervical cancer progression, it integrates into the host DNA [6]. Some of the genes can be disrupted in this process, but E6 and E7 remain highly conserved, as these are the main oncogenic proteins. E6 leads to the degradation of p53 [7] and E7 binds and inhibits the tumour suppressor, Rb [8]. This leads to an increase in p16 levels, which are normally negatively

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regulated by Rb [9]. P16 expression can be used as a surrogate marker of HPV positivity using immunohistochemistry.

However, over recent years it has become evident that E6 and E7 also inhibit multiple other cellular functions in addition to p53 and Rb and therefore HPV-associated oncogenesis is much more complex than previously thought. For example, E6 has been shown to interact with PDZ domain-containing proteins leading to their degradation [10]. Mutant cell lines in which E6 was unable to bind PDZ domains lost almost all tumorigenic ability. The PDZ domain-containing proteins that were responsible for this were SCRIB, MAGI1 and PAR3, which leads to loss of cell to cell contact and cell polarity. In addition, E6 activates transcription of telomerase reverse transcriptase and telomerase, thereby leading to immortalisation of epithelial cells [11].

As well as factors related to the virus itself, progression in HPV-associated cancers is also related to the host immune response. Immunosuppressed populations, such as people with AIDS or organ transplant recipients, have increased incidences of HPV-related malignancies [12]. Several human leukocyte antigen (HLA) types have been shown to either predispose to or protect against HPV-related cervical cancer [13,14] and are associated with prognosis in oropharyngeal cancer [15].

HPV-associated cancers accounted for 3% of cancers diagnosed in women and 2% of cancers diagnosed in men in the USA in 2009 [16]. Although the incidence rate of cervical cancer has been declining (due to the cervical screening programme and vaccination), the incidence rates of HPV-associated oropharyngeal, vulval and anal cancers increased from 2000 to 2009. It has been estimated that worldwide, between 1998 and 2003, HPV was associated with almost 100% of cervical cancers (70% of which are attributable to HPV-16 and -18), 35% of oropharyngeal cancers, 90% of anal cancers, 40% of vulval and vaginal cancers and 40% of penile cancers [17].

Although the incidence of HPV-related cancers should decline in the future due to HPV vaccination programmes, the main burden of disease particularly for cervical cancer is in Africa, India and China where vaccination programmes are yet to be implemented [18,19].

A systematic review has shown that since the introduction of HPV vaccination programmes in 2007 in high income countries, the rate of HPV-16/18 infection in girls has reduced by 68% (relative risk 0.32, 95% confidence interval 0.19–0.52) [20]. The rate of anogenital warts in boys <20 years has decreased (0.66, 95% confidence interval 0.47–0.91) in countries with vaccination uptake >50% but not in countries with a lower uptake [20]. It is too early to see a reduction in the incidence of HPV-related cancers due to the significant time-lag from HPV infection to the development of invasive cancer.

Clinical Outcomes and Prognostication Based on Human Papillomavirus Status

HPV status as a prognostic factor began to draw attention in 2010, when a study in oropharyngeal cancer patients undergoing chemoradiotherapy (CRT) showed significantly improved 3-year survival rates of 82% for HPV-positive cases versus 57% for HPV-negative cases ($P < 0.01$) [21]. Patients can be classified as low, medium or high risk depending on their HPV status, smoking history, tumour and node staging. HPV positivity has also been shown to be associated with a good response to radiotherapy alone [9] and induction chemotherapy [22]. The vast majority of HPV-positive oropharyngeal squamous cell carcinoma (OPSCC) are due to HPV-16 [23]. Non-oropharyngeal head and neck cancers can also be caused by HPV in 4% of cases, but these HPV-related cancers do not have a better prognosis [24]. This is due to lower levels of immune cell infiltration compared with OPSCC HPV-positive cancers.

As HPV-positive OPSCC patients have a better prognosis, there is much interest in whether these patients could receive less intensive treatment [25]. This approach would hopefully reduce late toxicity, such as dysphagia, while maintaining high overall survival rates. De-ESCALaTE HPV [26], RTOG 1016 [27] and TROG 12.01 [28] are addressing this issue by comparing standard cisplatin-based CRT with cetuximab and radiotherapy. There are some preliminary data in a small cohort of patients that HPV-positive patients had an improved disease-free survival (DFS) compared with HPV-negative patients receiving radiotherapy and cetuximab [29]. There are other methods of de-escalating treatment for these patients, such as using the response to induction chemotherapy to personalise radiotherapy dose and volumes, reducing radiotherapy doses for all patients receiving CRT or the incorporation of robotic surgery to allow less intensive adjuvant treatment (dose reduced radiotherapy with or without chemotherapy).

HPV status is less useful as a prognostic marker in cervical cancer as the vast majority of cervical cancers are HPV positive. Only 6% are truly HPV negative using polymerase chain reaction, but these patients do have a poorer DFS, 52 months versus 110 months, $P = 0.01$ [30]. HPV negativity is more common in adenocarcinoma than in squamous cell carcinoma (SCC; 16% versus 3%, $P = 0.017$). In multivariate analysis, HPV negativity and FIGO staging were associated with an increased risk of progression and mortality [30].

There is evidence to suggest that the HPV genotype may, however, be a useful prognostic marker in cervical cancer. HPV-18 positivity has a poorer prognosis in early stage cervical cancer [31]. The relative risk of death for patients with HPV-18 cervical cancer is 2.4 times greater than that of HPV-16 cervical cancers (95% confidence interval 1.29–4.59) [32]. In addition, HPV-18 and -58-positive cervical cancer patients may derive a greater benefit from the addition of concurrent chemotherapy to radiotherapy than HPV-16 and -33-positive patients [33]. To add further complexity, HPV-16 has four different variants, which may also have differing oncogenic potentials, with the non-European-like variant having an increased risk of progression to high grade cervical intraepithelial neoplasia (CIN) and invasive malignancy [34].

As well as HPV genotype, viral load has also been shown to be a strong independent risk factor in both cervical [35] and anal [36] cancers, with low viral load

predicting for poorer DFS. In these patients, there may be other factors or mutations driving oncogenesis as active viral replication is low. A decrease in viral load to >99.5% of baseline levels in response to treatment is associated with better survival outcomes in cervical cancers [37]. Datta *et al.* [38] analysed HPV titres in cervical smears taken weekly throughout radiotherapy for SCC of the cervix and showed that the mean TCD50 (tumour control dose for 50% regression) was 34 Gy in patients with a high HPV titre and 39 Gy for patients with a low HPV titre. They postulated that as radiotherapy progresses and the HPV titre decreases in the high HPV titre group, p53 and Rb function is restored and therefore these tumours become more radiosensitive.

Cell-free DNA is a way of detecting DNA derived from tumour in a patient's serum that allows a minimally invasive way of getting information about the genetics of the tumour. This could be used to guide targeted therapies and could also be used to monitor relapse or recurrence. The difficulty with other cancers is that it can be problematic to differentiate between tumour and host DNA, whereas in HPV-related cancers this is not an issue.

Cell-free HPV DNA can be detected in the serum of 93% of patients with HPV-positive cancers (cervical, anal and oropharyngeal) [39]. In cervical cancer, detection is correlated with poor prognostic features such as lymphovascular invasion, deep stromal invasion, nodal disease and larger tumours [40]. HPV DNA became negative after treatment in those patients without recurrent or persistent disease. Levels were found to rise in some patients up to 423 days (median 72 days) before recurrence being diagnosed [41]. Serum HPV DNA levels were higher in patients with metastases than in those with local recurrence [42]. In metastatic cervical cancer, HPV DNA was found in the serum of 100% of patients ($n = 19$) and the HPV genotype could be accurately identified from the serum sample [43].

In head and neck SCC (HNSCC) patients, elevated pretreatment HPV DNA levels are associated with a higher nodal and overall stage [44]. This can be used for monitoring purposes after CRT to assess whether there is residual disease [45]. In some patients, levels have also been shown to rise before recurrence is visible on computed tomography or magnetic resonance imaging. Positron emission tomography-computed tomography scanning was required to show the recurrence [46]. Cell-free HPV DNA has also been shown to be present in 88% of anal cancer patients before CRT, with higher levels being associated with node-positive disease [47]. Those patients who had persistence of serum HPV DNA had a shorter DFS.

Expression of certain HPV genes, such as E2, may also influence the response to treatment in both cervical and oropharyngeal cancers. The E2 gene is often disrupted on integration of viral DNA into the host DNA. E2 negatively regulates the expression of E6 and E7. However, in 39% of HPV-16-positive cervical cancers [48] an intact E2 gene was present, which was associated with a trend for an improved DFS. In oropharyngeal patients, only patients with a disrupted E2 gene had locoregional failure [49]. Increased radiosensitivity due to the expression of E2 has been confirmed *in vitro* [50].

HPV status has also been shown to be an independent prognostic factor in anal cancer [51,52], but given that 90% of anal cancers are p16 positive [53], additional methods for stratification have been investigated. HPV-positive patients can be stratified according to tumour infiltrating lymphocyte (TIL) counts. Absent or low levels of TILs had a recurrence-free survival rate of 63% compared with 92% for high levels of TILs [54]. PLATO is a UK trial currently recruiting anal cancer patients. One of the questions being asked is whether intermediate-risk patients due to have CRT could be dose de-escalated. Although this trial is not specifically for HPV-positive patients, HPV status and TIL counts will be measured prospectively.

Similar results have been shown in HPV-positive oropharyngeal [55] and cervical cancers [56]. In cervical cancers, high levels of T regulatory cells, low levels of CD4+ cells and a low CD4/CD8 ratio were associated with a poorer clinical outcome [57]. Similarly, in OPSCC, HPV-positive tumours had higher numbers of TILs and T regulatory cells compared with HPV-negative tumours [58,59]. A high number of T cells was correlated with an improved DFS in HPV-positive OPSCC [58].

Interestingly, 4% of HNSCC outside of the oropharynx have been found to contain HPV DNA (and are therefore HPV positive) but improved survival is only associated with HPV-positive cancers in the oropharynx. Gene expression and methylation is similar for HPV-positive HNSCC regardless of the site. However, the immune microenvironment is different, as there are higher levels of TILs in HPV-positive OPSCC compared with HPV-positive non-OPSCC. There also appears to be a distinct B cell signature in HPV-positive OPSCC that is lacking in HPV-negative OPSCC [60].

For vulval cancer, high-risk HPV has been found in 52% of cases (32/62) [61]. HPV positivity in vulval SCC was associated with improved progression-free survival disease (hazard ratio 0.32, $P = 0.02$) [61] and a lower risk of recurrence [62,63]. In a meta-analysis of penile cancer trials, 27% of patients were HPV positive and they had an improved disease-specific survival (hazard ratio 0.61, 95% confidence interval 0.30–0.69) [64].

Another inherent difference between HPV-positive and HPV-negative cancers is the activity of the apolipoprotein B mRNA editing enzyme catalytic polypeptide-like (APOBEC) protein pathway. APOBEC proteins are cytidine deaminases with high specificity for single-stranded DNA that may be exposed during replication or transcription. They convert cytosine to uracil on DNA or RNA. DNA repair pathways then usually convert the resulting uracil to thymine or guanine. APOBECs have roles in innate and adaptive immunity to various viruses, including HPV. APOBEC mutation signatures have been found in HPV-positive precancerous lesions of the cervix [65] and E6 has been shown to be able to upregulate APOBEC3B activity [66]. Over-activity of APOBEC proteins has also been found in many different cancers, including cervical and HNSCC [67], with APOBEC mutations being more prevalent in HPV-positive compared with HPV-

negative HNSCC [68]. However, there are many members of the APOBEC family and although some may lead to increased mutagenesis and progression, others (such as APOBEC3A and 3G) may have anti-viral and anti-cancer properties by inhibiting E6 and E7 [69,70].

A high mutational burden has been shown in lung [71] and colorectal [72] cancer to be associated with improved responses and survival to immunotherapy such as PD-1 blockade. The pathway to increased mutational burden could either be due to DNA repair pathway impairment [72] or due to increased APOBEC activity [73], both of which could lead to increased production of neoantigens, which can be presented to cytotoxic T cells on major histocompatibility complex proteins on the tumour cell surface. Immunotherapy could then be used to enhance the response of these cells to the tumour.

Pre-clinical Evidence of Differences Between Human Papillomavirus-Positive and -Negative Tumours

With the incidence rates of certain HPV-positive cancers increasing, interest in the differences between HPV-positive and -negative cancers continues to grow (see Figure 1). In defining these differences, it may allow management to be guided by HPV positivity or even genotype in the future.

HPV-positive HNSCC cell lines have been shown to be more radiosensitive than HPV-negative cell lines both *in vitro* [74] and *in vivo* [74,75]. HPV-positive cell lines have a prolonged G2/M cell cycle arrest and increased rates of apoptosis mediated by increased p53 levels 24 h after radiation [75]. Therefore, even though E6 leads to degradation of p53, the low levels of normal p53 in HPV-positive cells can still be activated by radiation. In HPV-negative head and neck cancers there are often mutations in p53, leading to its inactivation [76] and, therefore, relative resistance of these cancers to treatment.

This has been supported by work from The Cancer Genome Atlas, which has profiled a large number of HNSCC cases and has shown that there are differences in the somatic genomic alterations between HPV-positive and HPV-negative cancers [77]. HPV-positive HNSCC predominantly has mutations in PIK3CA, loss of TRAF3 and amplification of E2F1, whereas HPV-negative HNSCC has almost universal loss of TP53 and CDKN2A (the gene encoding p16) and amplification of 11q22. A similar study in anal cancer has shown that the most frequently mutated genes in HPV-positive cases were PIK3CA, FBXW7, PTEN and TP53 [78]. HPV-negative anal cancers had more frequent TP53 and CDKN2A mutations. In cervical SCC, common mutations are found in FBXW7, PIK3CA, MAPK1, HLA-B, STK11, NFE2L2, PTEN and EP300 [79]. Therefore, mutations in the P3IK/AKT/mTOR pathway are common in these three malignancies, but are not confined to the HPV-positive population, whereas mutations in TP53 and CDKN2A are almost exclusive to HPV-negative patients. Lower p53 expression occurs in HPV-positive cancers due to increased degradation rather than mutation, which may underlie the differences in radiosensitivity and prognosis.

Another possible explanation for the increased radiosensitivity of HPV-positive cancers is the interference of viral proteins E6 and E7 with DNA repair mechanisms. This can lead to increased chromosomal instability [80], which may be advantageous in the transformation process, allowing the tumour to acquire more oncogenic mutations [81]. However, reduced DNA repair after irradiation can lead to mitotic catastrophe and cell death.

HPV-positive HNSCC cell lines accumulate more double-stranded DNA breaks than HPV-negative cell lines and this correlates with the degree of G2 arrest and radiosensitivity [74]. HPV-positive cell lines were shown, both *in vitro* and *in vivo*, to have more γ—H2AX foci (which identify sites of double-stranded DNA breaks) 24 h after a single 2 Gy dose of irradiation compared with HPV-negative HNSCC cell lines [82]. E7 expression in immortalised normal oral epithelial cell lines leads to delayed resolution of γ—H2AX foci and delayed DNA damage repair.

The precise mechanisms as to how HPV proteins dysregulate DNA repair are not fully elucidated and are probably complex and multifactorial. Rb is known to have a direct role in non-homologous end joining [83]. E6 also dysregulates non-homologous end joining via p53-dependent and -independent mechanisms [84] and overexpression of p16 affects homologous recombination by impairing the recruitment of Rad51 to sites of DNA damage [85]. In HNSCC, Rad51B is a common HPV integration site, leading to its inactivation and impairment of homologous recombination [86].

There is also a link between hypermethylation of various DNA repair genes and expression of immune checkpoint proteins (cytotoxic T-lymphocyte-associated protein 4 [CTLA-4] and programmed death ligand 1 [PD-L1]) in HNSCC, lung SCC and cervical SCC. Hypermethylation of Rad51B was shown in all three cancers to correlate with increased expression of both CTLA-4 and PD-L1 and hypermethylation of XRCC3 (also involved in homologous recombination) correlated with increased CTLA-4 expression in all three cancers [87]. The HPV E7 protein itself has also been shown to drive PD-L1 expression [88]. In addition, recent evidence has shown that E6 and E7 can lead to hypermethylation and silencing of various immune genes, such as type 1 interferons, HLA-E and CXCL14 [89]. This evidence therefore provides a link between HPV positivity, DNA repair deficiency, radiosensitivity and the host immune response in these cancers.

As well as differences in inherent radiosensitivity between HPV-positive and HPV-negative tumours, there are also differences in the tumour microenvironment. Experiments in immunocompromised mice using different cervical cancer cell lines have shown that HPV-positive cell lines (SiHa and HeLa) are more efficient at recruiting leukocytes than C33A, which is HPV negative [90]. Leukocytes, particularly lymphocytes, are important for mounting an anti-tumour immune response. HPV-positive cell lines also expressed higher levels of IL-6, IL-8 and CXCL1 (which can induce myeloid cell proliferation), whereas the HPV-

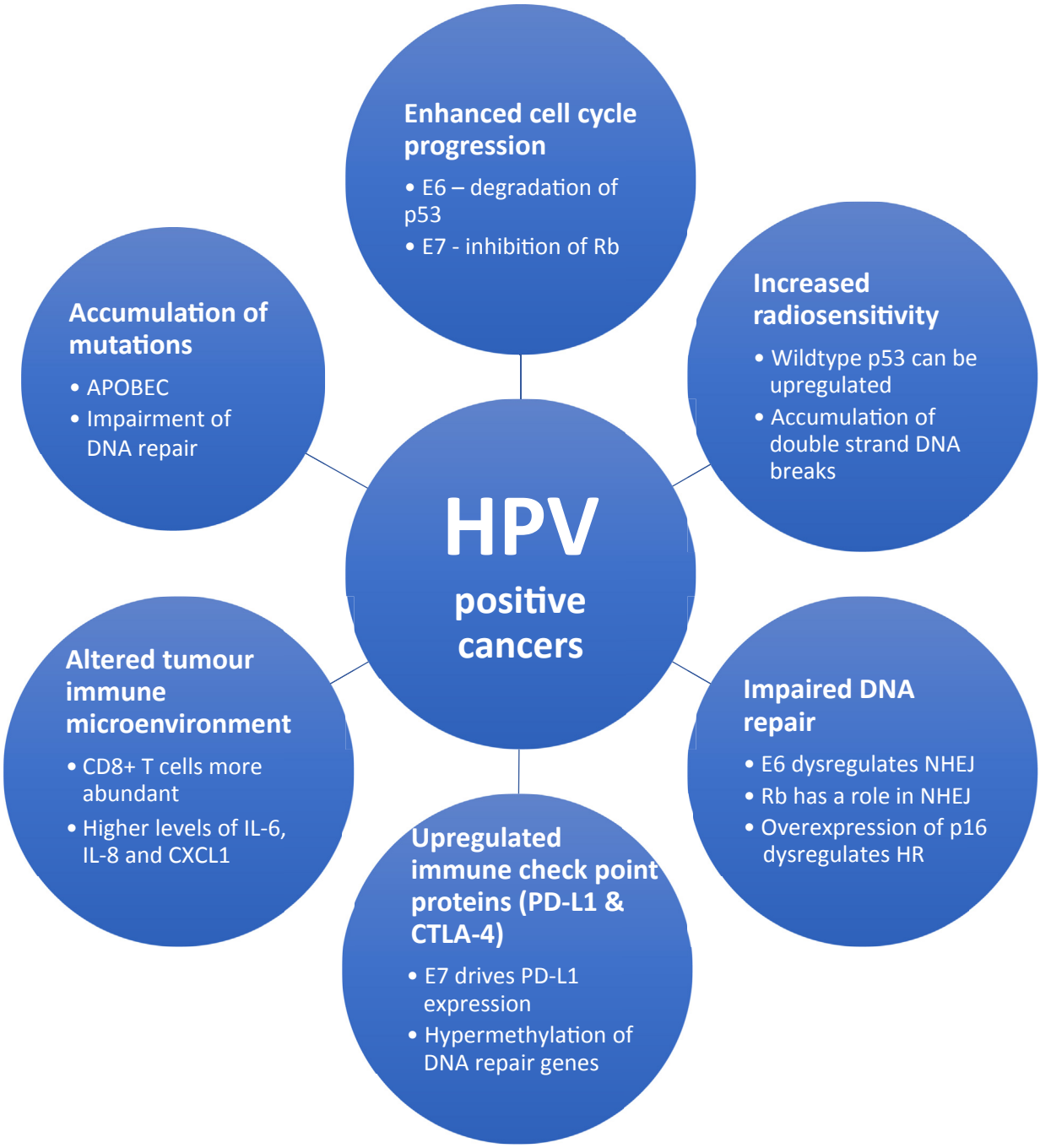

Fig 1. Flow chart to highlight some of the unique features common to human papillomavirus (HPV)-positive cancers. There is a significant and complex interplay between the different mechanisms, such as impairment in DNA repair contributing to the inherent radiosensitivity of these cancers and upregulation of checkpoint proteins. Additionally, the accumulation of mutations leads to the formation of neoantigens, which can alter the tumour microenvironment by promoting a CD8+ immune response. E6 and E7, sixth and seventh early genes of the HPV genome; NHEJ, non-homologous end joining; HR, homologous recombination; PD-L1, programmed death ligand-1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; T reg, regulatory T cell; CXCL1, chemokine ligand 1; APOBEC, apolipoprotein B mRNA editing enzyme catalytic polypeptide-like protein pathway.

negative cell line expressed higher levels of IL-16 and IL-17. However, despite the higher levels of IL-6 and IL-8, phosphorylation levels of STAT3 and NFκB in lymphocytes associated with HPV-positive tumours were very low, indicating that although these cells were abundant, they were inactive. The tumour microenvironment has also been shown to differ between HPV-positive and -negative HNSCC, with tumour infiltrating CD8+ T cells being more abundant than in HPV-positive HNSCC [91].

Despite the pre-clinical evidence for alterations in radiosensitivity and the tumour microenvironment in oropharyngeal and cervical carcinomas, there is a lack of evidence in anal carcinoma. This is due to a lack of anal SCC pre-clinical models and cell lines. In 2009, the establishment of the

Table 1
Human papillomavirus (HPV) positivity and programmed death ligand-1 (PD-L1) expression in various cancer sites

Tumour site	HPV-positive rate [17,30]	PD-L1 expression		
		All patients	HPV-positive patients	HPV-negative patients
HNSCC [94]	35%	59%	70%	29%
Cervical cancer [95,96,98]	94%	44–54%	NS	NS
Anal cancer [97]	90%	56%	NS	NS
Penile cancer [99]	40%	62%	NS	NS
Vulval cancer [100]	40%	32%	NS	NS
Vaginal cancer	40%	NS	NS	NS

HNSCC, head and neck squamous cell carcinoma; NS, not specified.

first anal SCC cell line was reported (SaTM-1), which was isolated from a lymph node metastasis of a patient undergoing an inguinal lymphadenectomy [92], but the HPV status of this cell line was not reported and to date there are no published studies using this cell line.

Immunotherapy in Human Papillomavirus-Positive Cancers

The mainstay of treatment for locally advanced HNSCC, cervical, vulval and anal cancers is CRT. This treatment approach offers good cure rates and organ preservation. However, a significant proportion of patients have persistent or recurrent disease, which can be difficult to treat. The basis of immunotherapy is to boost the host immune response against the tumour. Programmed cell death-1 (PD-1) is expressed on activated T cells and binds PD-L1 or PD-L2 on tumour cells or other immune cells to suppress T cell activation and therefore promote immune evasion [93]. Seventy per cent of HPV-positive HNSCC tumour samples express PD-L1 at the cell surface compared with 29% of HPV-negative tumour samples [94] (see Table 1). In cervical cancer, about 50% of SCC express PD-L1 [95,96] and in anal cancer 56% [97]. HPV replication leads to PD-L1 expression on the cell surface of cervical cancer cells [95].

Nivolumab is a fully human antibody that blocks PD-1 and has been shown to be effective in melanoma [101], advanced lung cancer (both squamous [102] and non-squamous [103]) and advanced platinum-resistant head and neck cancers [104]. HNSCC patients had an improved overall survival with nivolumab compared with standard chemotherapy, regardless of their PD-L1 or p16 status. However, there was preliminary evidence that patients with PD-L1 expression $\geq$1% or p16-positive tumours (indicating HPV positivity) may derive greater benefit from nivolumab [104]. In KEYNOTE-012, a phase Ib trial, 78% of biopsies from recurrent or metastatic HNSCC patients were PD-L1 positive [105]. The overall response rate to pembrolizumab was 25% in HPV-positive patients compared with 14% in HPV-negative cases. Nivolumab has been shown to have a disease control rate of 79% in previously treated metastatic SCC of the anus [106] and pembrolizumab has a disease control rate of 58% in a similar group of patients [107].

In the cervical cancer cohort of KEYNOTE-028, 17% of patients achieved a partial response and 13% had stable disease [108]. In the partial responders, the median duration of response was 5.4 months.

Immunotherapy, therefore, has shown great promise in multiple tumour types, but the response rate is often in the region of 20% [109]. Of the patients who do respond, many can have long-term survival and therefore there is much interest in identifying these patients using prognostic and predictive biomarkers. PD-L1 expression is not a perfect biomarker, partly for technical reasons, such as tumour heterogeneity, and also because some patients with PD-L1 negativity can still have a response to PD-1 blockade [110]. Checkmate 358, for example, reported objective response rate (ORR) of 26.3% for nivolumab in cervical cancers irrespective of PD-L1 or HPV status [111].

In melanoma, the best predictive marker in pre-treatment samples was CD8+ counts at the invasive margin, which highlights the need for immune cells to be present within the tumour for PD-1 inhibition to be effective [112]. As previously mentioned, total mutational burden (TMB) has also been shown to be associated with response to immunotherapy in melanoma [113] and lung cancer [71]. HNSCC and cervical cancers have reasonably high TMB, being ranked just behind melanoma, lung, bladder and oesophageal and colorectal cancer [67]. The importance of a higher TMB is that it is correlated with a higher level of neoantigens, which can illicit an immune response when presented to CD8 cytotoxic lymphocytes in an immunostimulatory microenvironment. In HPV-related cancers, the antigens that drive these immune responses appear to be both viral and non-viral [114]. The future of immunotherapy will probably involve combination therapy to promote TIL infiltration into tumours, activation of TILs and subsequent cytotoxicity. Therapeutic vaccines are also being developed, for example, using live vectors such as *Listeria monocytogenes* to stimulate T cell immunity using a HPV–E7 fusion protein [115].

Conclusion

HPV is implicated in a significant proportion of oropharyngeal cancers as well as most cervical and anal cancers. These cancers have a better prognosis compared with their HPV-negative counterparts and therefore represent a separate entity with a different underlying pathogenesis. Some of these differences are related to impaired DNA

repair pathways, increased APOBEC activity and an altered tumour microenvironment. The prevention of HPV infection with the commercially available HPV vaccinations has been very successful, but the vaccines are not effective against established infection. Evasion of the host immune response by virus-infected cells allows progression of these cancers and, therefore, immunotherapy with checkpoint inhibitors is an attractive therapeutic option. The future management of HNSCC, cervical and anal cancers will probably involve treatment stratification based on HPV status or even HPV genotype, allowing either deintensification for good prognosis tumours or the addition of immunotherapy to boost the host anti-tumour response in poorer prognosis tumours, although further research is needed before this can be brought into clinical practise.

Conflict of interest

The authors declare no conflict of interest.

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