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SKIN CANCER AND HUMAN PAPILLOMAVIRUS

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Abstract
Skin cancer (SC) is the one of the widespread kind of cancers worldwide. Among other risk factors, Human Papillomavirus (HPV) is the potential causative agents for skin tumorigenesis. In previously scientific published research, the underlying role of HPV remained controversial about which kind of HPVs are involved on the onset initiation and progression of non-melanoma skin cancer (NMSC) such as squamous cell carcinoma (SCC), basal cell carcinoma (BCC) and malignant melanoma (MM). Apha and beta HPV have been found with the course and development of keratinocytes mutation and skin tumor malignancies. The pathogenicity of HPV lies in its oncogenic proteins such as E6 and E7 belong to Beta HPV kind along with various other transcriptional factors. E6 and E7 are found to deregulation in the tumor suppressor genes p53 and pRb to disturb normal activity of cell cycle and to help metastasize skin cancer. There are also increasing evidences of weakened immune system in melanoma and non-melanoma skin cancer patients associated with human papillomavirus. The combined influence of ultraviolet radiations (UVA and UVB) has detected with human papillomavirus to trigger and promote melanoma and non-melanoma skin cancer development. These results in altered chromosome structure, uncontrolled S-phase, and inhibit apoptosis to advance skin carcinoma. This review article summarizes not only previous arguments for the involvement of oncogenicity of HPVs strains with skin cancer types but also demonstrates an extensive review of the significant previously published data that were not covered yet.

Keywords: Skin Cancer, Human Papillomavirus, Melanoma, Non-melanoma Skin Cancer, p53

Skin Cancer

Skin cancer involves the uncontrolled multiplication and proliferation of skin cells, which can metastasize to other body parts. It develops when the DNA of skin cells is damaged and is left impaired. This damage ultimately comes up with mutations, genetic defects, unchecked multiplication of skin cells and the formation of malignant tumors. This type of cancer mostly occurs when unrepairable DNA damage to cells of the skin occurs as a result skin cells multiply rapidly and form tumors which might be benign or malignant [1]. Fair-skinned individuals have greater chances of having skin cancer than individuals the dark skin color. Skin cancer incidences are quite lower among Asian people than the Western people. There is worldwide concern about the increase in the incidence of skin cancer [2]. Skin cancer develops from several factors including genetic as well as environmental factors. Environmental factors include UV exposure and solar exposure. Genetic factors include red hair, fair skin; family history and lack of tanning ability. Several epigenetic events contribute to skin cancer progression including histone modification, micro-RNA expression and methylation of genomic promoter region [3].

Skin cancer being one of the most emerging and distressing diseases is dominant in fair and light-skinned populations all over the world. Its prevalence is increasing cogently and thus posing a great threat to the health of the public. It is more common in Caucasians as compared to Americans and Africans. As skin is the largest organ of our body skin malignancies account for 20-30 % of all other body malignancies. In the Asian population including Pakistani population incidence of skin cancer is less as compared to the Western world [4]. Skin cancer is a significant form of cancer as it contributes to 3 million newly diagnosed non-melanoma cases and around 123,000 melanoma cases all over the world. Major risk factors linked with skin cancer are ultraviolet radiations, weak immune system, family history, genetic, environmental and viral infection such as human papillomavirus [5]. In this review article, we will summarize previous data and recent information on detail association of human papillomavirus with skin cancer.

Human Papilloma Virus (HPV)

The non-enveloped, icosahedral, 50–60 nm-diameter HPVs are tiny viruses. The genome has up to eight open reading frames (ORFs) and is made up of a double-strand helical DNA. HPV genome has between seven thousand to eight thousand nucleotide base pairs [6]. The human community is extensively infected with human papillomavirus. Animals such as birds and mammals are commonly infected with human papillomaviruses (HPVs), which are members of the Papillomaviridae family and invade the keratin cells of the skin and epithelium [7]. An estimated 170 HPV kinds have been thoroughly described and identified at various body locations to far, and this total is still rising. The three primary parts of the HPV genome are as follows: (1) the upstream regulatory region (URR), thereby serves as a promoter as well as includes transcriptional component adhering points that govern the virus's regulation of gene expression; (2) the initial transcription part (E), which is composed of six genes with various activities, such as virus repetition and cell evolution; the E1 and E2 genomes in these parts are copied throughout the initial phases, whereas the E6 and E7 genetic material are further concerned in the oncogenicity of the virus; in addition (3) the late transcription part (L), which generates the proteins L1 and L2 that auto-assemble to produce the cap [8]. In conclusion, two controlling proteins (E1 and E2) regulate transcription and copies, three cancer genes (E5, E6, and E7) regulate the development procedure, and two building proteins (L1 and L2) construct the viral genome coat. With the several family members, the URR and proteins E1, E2, L1, and L2 are especially well-conserved. Within the higher layers of the epithelium, the transcription of viral genes transitions regarding the production of L2 and L1 capsid protein. These proteins are directed to the nucleus and spontaneously organize into virions, which enclose the viral genome [9]. Ultimately, the process of viral discharge occurs without the rupture of the host cell. Among the several forms of HPV, the proteins E1, E2, L1, and L2 are the most well-preserved components in the URR [10]. The L1 ORF gene is used as a standard for the phylogenetic categorization of HPVs. The viral pathogenic lifecycle is intricately connected to the developmental programmed of the skin cells [11]. The virion infiltrates basal keratinocytes via micro wounds or hair shafts. Transmission

can occur without the virus being in the shape of a full viral particle. Skin friction and accessibility to the exposed viral genome can replicate the entire endogenous progression of an illness in many animal studies. Following a full proliferative phase, the bare viral DNA is integrated into the cell's nucleus and multiplies as episomes. The E1 and E2 viral proteins are responsible for maintaining the functionality of the genome and ensuring its proper distribution to the resulting cells [12].

Typically, when keratinocytes proceed forward to initiate the course of development, they cease replication and experience a sequence of transformations until they constitute the epithelial stratum [13]. The E6 and E7 proteins exploit the barrier systems and enable the keratinocytes to undergo unregulated growth. To be more precise, the E7 protein selectively attaches to the retinoblastoma protein (pRb) and stimulates its activation. This leads to the liberation of the E2F element, which then triggers the unregulated relapse into the S-phase of the cell cycle [14]. On the other hand, the E6 protein causes the destruction of p53. The HPV E6 and E7 proteins play a role in modifying the regulatory processes, altering the structure of chromosomes, and influencing the production of miRNA [15]. This leads to the disruption of genes that inhibit cancer and cancer-causing genes, ultimately resulting in the alteration of keratinocytes. The E5 protein ultimately stimulates excessive cell growth, inhibits programmed cell death in damaged cells, and is probable to aid in the development of cancerous growth [16]. All the remaining proteins function as cofactors in this pathway. Following the development of keratinocytes, the E6 and E7 proteins are substituted by E1, E2, E4, and E5, resulting in a significant rise in the viral replication count to hundreds of thousands each cell. Proteins E6 and E7 function as cancer-causing proteins in dangerous kinds, yet not in relatively safe kinds [17].

In another study mutual linkage connecting pRb and p16 was discovered, elucidating increased levels of p16 in malignancies and precursors of cervical tumors that are linked to HPV contamination [18]. Regarding β-HPVs, the function associated with proteins E6 and E7 differs from that of α-HPVs. Rather, it entails the breakdown of Bcl-2 [19]. The hair shafts are considered the primary source for epidermal β-HPVs. HPV can be found in hair shafts located in several areas of the body, such as the head, foreheads, limbs, abdomen, thighs, and pelvic zone [11]. The variety of β-HPV kinds found in eyelid hair shafts is highly indicative of various areas of the organism, implying a ubiquitous over the entire epidermis. Consequently, eyelid hairs were utilized as a readily obtainable indicator in numerous contemporary clinical investigations [20].

HPV is classified into three distinct types: beta, gamma, and alpha [21]. The emergence of SCC is associated with the presence of HPV-type beta. Beta HPV possesses an impact in the development of squamous cell carcinoma malignancies by altering the cell phase and DNA reconstruction mechanisms [22]. SCC is also associated with HPV type alpha. HPV77 is an alpha form of HPV that is identified in individuals with weakened immune systems. HPV77 possesses a p53 DNA binding location, which develops in response to exposure to UV radiation [23]. p53 enhances the HPV77 promoter's functionality, leading to the production of E7 and E6 proteins. These proteins subsequently disrupt the p53 and Rb inhibitor mechanisms [24]. The potential mechanism of skin tumorigenesis by human papillomavirus through its all possibilities can be shown in given figure. 1.

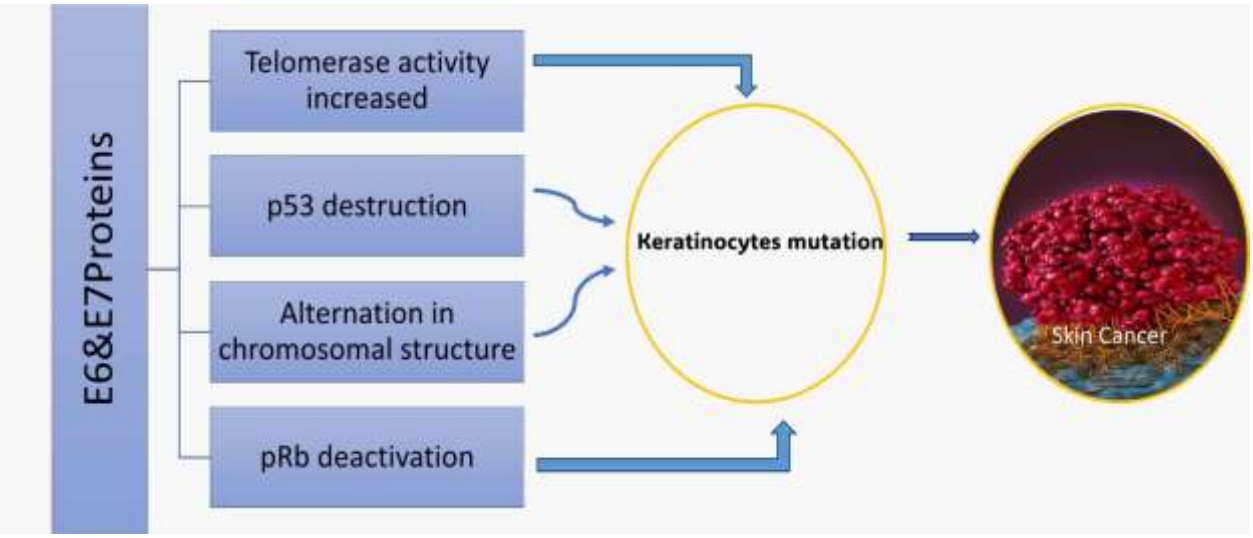

Figure 1: Possible potential ways that how Human Papillomavirus infects and causes skin cancer along with all types through its E6 and E7 proteins. All of these mechanisms and pathways are resulted in keratinocytes mutation that consequent in skin cancer.

The carcinogenic function of certain mucosal HPVs has been proven in various epidermal malignancies affecting the anogenital and superior respiratory routes [25]. However, the causal connection among particular HPV kinds and non-melanoma skin cancers, such as squamous cell carcinoma and basal cell carcinoma, is still not well understood [26]. Several demographic studies have established a connection connecting indicators of beta-HPV contamination and SCC in individuals with epidermodysplasia verruciformis (EV) and in those who have received organ transplants. There is increasing proof suggesting that beta-HPVs may contribute to the development of non-melanoma skin cancer in humans in general, including those with a normal immune system. The exact processes by which beta-HPVs contribute to the development of cancer have not been determined lately. One possibility that might be considered could be that beta-HPVs might hinder the natural protection mechanisms of host cells versus ultraviolet radiation, hence disrupting the processes of DNA repair and apoptosis [27]. The "hit and run" idea is supported by the fact that cancerous components have a reduced viral burden compared to forerunner disorders like actinic keratosis (AK). This idea suggests that the virus is involved in the initial phases of cancer development but is not required for the continued growth of cancerous cells [28]. Most research on the involvement of HPV in non-melanoma skin cancers has primarily concentrated on squamous cell carcinomas. However, there is a scarcity of publications examining HPV infection in basal cell carcinomas. Basal cell carcinoma is the predominant form of skin cancer and has had a global rise in occurrence in recent times [29]. Exposure to ultraviolet radiation (UVB) is the primary risk factor for basal cell carcinoma among people with vulnerable skin texture and a certain biological predisposition. The exact mechanism by which HPV contamination contributes to the development of BCC is not well comprehended. The incidence of beta-HPV was greater in participants with SCC compared to those with BCC. No HPV types were found in the mucosa or vaginal areas [30]. The highest incidence of contamination seen in non-melanoma skin cancer, specifically in the BCC demographics, was caused by Beta-HPV strains from genus 1. HPV types 5, 8, 24, and 93 were the most often identified in collections from participants with BCC, comprising 41% of all illnesses. The tumor patches showed no substantial difference compared to the surrounding epidermis in terms of the cumulative occurrence of beta-HPV transmission and the variety of viral strains found in associated samples [31]. Nevertheless, beta-HPV kinds originating from species 1 exhibited a notably elevated occurrence in BCC specimens, that was further distinguished by a greater prevalence of repeated lesions. The findings of our study indicate that beta-1-HPVs, along with the presence of many virus types, may have a significant role in the development of NMSC, namely BCC [26].

The process of tumorigenesis is thought to be linked to the modifying properties of E6 and E7 proteins, particularly those derived from beta HPV strains. The oncoproteins are mainly accountable

for disrupting the cell cycle, leading to the malignancy of cells contaminated with HPV. The E6 and E7 proteins immortalize human keratin cells by effectively decreasing the p53 and pRb mechanisms. The proliferation of HPVs in developing epidermal tissues leads to an elevated activity of the E6 and E7 oncoproteins [32]. The consistent finding may be attributed to a rise of epidermal HPV multiplication in an environment of sunlight (UVR). Specifically, research has shown that UV light access can enhance the regulator ability of the noncoding section of epidermal form HPV. The concept of a hit-and-run event has been proposed as an essential component in the initial phase of tumorigenesis. By impeding the procedure of repairing DNA destruction caused by UVR, the accumulation of DNA fragments and alterations occurs. Consequently, the presence of E6 and E7 proteins becomes unnecessary for sustaining the malignant characteristics in subsequent phases [33]. MM and NMSC continue to be prevalent forms of carcinoma across the globe. The research discovered that persons who have previously been diagnosed with HPV transmission possess a greater chance of acquiring equally melanoma and nonmelanoma skin cancer relative to the overall demographic. This finding takes into account factors such as sex, other medical conditions, and medications that could potentially influence the results. As individuals with HPV contamination grow older, their probability of acquiring skin malignancies increases [34]. In the Cox proportional hazard regression model, the presence of illnesses had not a meaningful impact on the occurrence of skin malignancies, with the exception of high blood pressure. Nevertheless, one stratified study uncovered that the presence of HPV contamination continued to demonstrate a clear association with the development of skin malignancies across all ages, gender, and comorbidity groupings, with a particularly notable risk shown in the 41-50 age range. Time-to-event assessment revealed a significant correlation involving HPV contamination and skin malignancies occurring during a period of 1-5 years of monitoring. This association may be attributed, at least in part, to the higher frequency of contacts to the dermatology clinic. Clients who have had past diseases affecting the skin are inclined to develop skin malignancies contrasted to individuals who have had diseases affecting the mucous membranes [35]. The comprehension of the correlation of MM and HPV was fundamental. Clinical data indicates a notable rise in the occurrence of epidermal melanoma, particularly in European people. This rise may be attributed to the infections of follicular hair melanocytes in biopsies by HPV. A prior investigation on the emergence of melanoma revealed a potential association with HPV and proposed a decrease in HPV 18E6/E7 expression and an increase in the stimulation of the p53 as well as Rb mechanisms [36].

The relationship between NMSC and HPV contamination has been extensively examined in earlier research. During a prior examination of skin biopsies including several cancer-causing viruses that affect epithelial cells, it was shown that the identification of HPV was prevalent in non-melanoma skin cancer cases relative to noncancerous biopsies. This finding provides evidence for the involvement of HPV transmission in the formation of NMSC [37]. Alpha papillomaviruses, particularly HPV 16, are widely acknowledged as dangerous kinds of HPV that may trigger anogenital, forehead, and neck malignancies. The case study of coloured Bowen's disorder also verified the existence of high-risk HPV strains. The connection involving dangerous HPVs and skin malignancies is difficult to establish [38]. An alternative explanation for the favourable outcome observed in our investigation is that persons who get sick with mucosal variants might exhibit increased susceptibility to developing epidermal variants as a consequence of an imbalanced immune system. A plausible explanation supports the connection involving high-risk HPV strains and non-melanoma skin cancer in the head and neck area. This research incorporates the malignant skin carcinoma occurring in the head and neck region as the main result measure. Earlier research has examined the correlation involving risky HPV and a specific group of head and neck cancers (HNC). In a prior investigation on HPV integration in HNC, it was found that 25 out of 35 cases of HNC exhibited an incorporation of risky HPV (specifically types 16, 33, or 35) into the human genome [39]. A separate study found that the combined prevalence of risky HPV specifically type 16 in oral squamous cell carcinoma were 39%. Therefore, additional research is needed to clarify the contribution of dangerous varieties to the development of non-melanoma skin cancer in the head and neck area [40].

Regarding the relatively low-risk HPVs, epidermal HPVs are widely spread on normal skin and can be a natural part of the normal bacteria in both those with weakened immune systems and those with damaged immune systems. There is increasing information suggesting that beta HPVs play an essential part in the development of non-melanoma skin cancer among epidermal HPVs. Beta HPV varieties contribute to the hit-and-run process by worsening the buildup of genetic changes caused by sunlight and serving as the catalyst for commencing tumor development in NMSC [41, 42]. A current histopathology investigation emphasized the significant incidence of oral HPV in NMSC. This suggests that active illnesses, as determined by E6 expression, are linked to the impairment of p53 activity. These data suggest that different kinds of HPV contribute to the development of NMSC. Although we were unable to accurately identify the specific type of HPV infection in our investigation, the positive findings provide clinical information that supports the earlier concept regarding the causal relationship between HPV disease and the increased likelihood of NMSC [43].

Sun exposure is well recognized as the key contributory determinant in the development of melanoma, although the potential role of viral causes in melanoma has received less attention. The involvement of HPV in the progression of melanoma was uncertain. Past research has shown that there is variation in the rate at which HPV is diagnosed in melanoma. In certain instances, dangerous HPV viruses, specifically HPV16, have been identified, suggesting that dangerous epithelial HPV16 may be involved in a specific subset of melanoma instances [44]. In relation to beta HPV, the presence of melanoma was considerably higher in type 22 but lower in type 21 compared to regular skin in the control group. A fascinating instance of vaginal melanosis was seen in a young woman who was contaminated with relatively safe HPV strains. In a prior investigation into the molecular basis of HPV 18 in the formation of uveal melanoma (UM), scientists showed that reducing the activity of HPV 18 E6/E7 resulted in a cessation of proliferation and the blocking of the cell cycle [45]. This was achieved by stimulating the p53 and Rb mechanisms. Although currently is a potential for viral DNA contamination in living organisms, evidence firmly indicates that HPV has a substantial influence on the development of UM. Nevertheless, given the limited frequency of instances and the absence of convincing discoveries, the researchers were unsuccessful in establishing a definitive correlation between HPV contamination and melanoma in our investigation. This investigation offers only restricted knowledge regarding the speculative association between HPV contamination and the development of melanoma [46].

On the other hand, since UV radiation is a widely recognized potential agent that increases the risk of melanoma, it is quite plausible to suggest that UV rays could result in a weakened immune system, which in turn initiates melanoma and/or HPV contamination. However, the concurrent occurrence of HPV contamination and ultraviolet (UV) rays would possibly confound their "responsible connection" [47]. Multiple investigations have demonstrated that the E6 protein derived from β-genus HPV reduces the levels of two crucial UV-repair kinases, namely ATM and ATR. The research proposed suggested the reduced accessibility of ATM and ATR affects the cells' capacity to defend against UV degradation. Under these circumstances, the combined impact of ultraviolet radiation can arise as a consequence of a previous HPV illness [48]. The comprehension of the origin and cause of ALM is basic, ambiguous, and subject to disagreement. The cause of this condition is likely to be influenced by multiple factors, particularly the interplay between tiny variations in genetics and specific ecological causes, like trauma. Furthermore, our database lacks details pertaining to Ultraviolet or sunshine involvement. Thus, our study does not provide a clear determination of the likelihood of UV-induced melanoma and/or HPV transmission [49].

The recent research focused on the captivating relationship between age diversity and the susceptibility to skin malignancies. The previously age group among 14 and 30 years exhibited a significant prevalence of skin cancer. The majority of individuals in the research investigation were under the age of 50, likely due to the fact that HPV contamination primarily impacts younger individuals. The impact of HPV contamination on the occurrence of skin malignancies appeared increasingly significant with advancing age in a Cox regression model. This stratification study revealed a significant risk of getting skin malignancies in the HPV cohort, particularly among individuals aged 41–50 years. Substantial data has demonstrated a rise in the elderly group affected

by HPV-positive NMSC. The prevalence of HPV16 among individuals with HPV-positive oropharynx squamous cell carcinoma varies depending on the age category [50, 51]. Regarding melanoma, past research uncovered distinct disparities in risk variables, including familial background, ultraviolet contact, and past experience with blisters, between teenage people and middle-aged individuals. In addition to the previously proposed theory of immunodeficiency which suggests that the reinstatement or delayed onset of HPV-positive skin cancer could be responsible, the rising number of elderly people and the higher prevalence of HPV illnesses among them might additionally contribute to rising numbers aged patients. Furthermore, it appears that senior individuals exhibit reduced rates of HPV elimination compared to younger individuals, therefore indicating a potential increase in cancer development in the aged demographic. This data aligns with a major alteration in statistical patterns of HPV-positive skin malignancies across different age groups [52].

HPV and Non-Melanoma Skin Cancer

NMSC is among highest prevalent kind of malignancy found in individuals with light-colored skin that encompasses BCC and SCC. UV rays represents the leading threat component, suggesting that alterations caused by UV rays play a significant impact in the development of NMSC. Additional variables have been proposed to play a role in the development of NMSC, specifically viral infections. The higher occurrence of NMSC in people with weakened immune systems, as opposed to those with normal immune function, indicates that the body's defenses play an essential part in this disease [53]. BCC represents around 75% of all NMSC instances in overall people, whereas SCC contributes around 25%. In kidney transplant subjects, the proportion of BCC to SCC seems to favour SCC when contrasted with individuals with a normal immune system. Additionally, there is a significant occurrence of numerous, severe infections in these individuals. Nevertheless, the prevalence of NMSC among Asians is steadily rising based on the present circumstances [54]. A new investigation conducted in Pakistan has revealed that BCC constitutes one of the predominant cancers, closely preceded by SCC. NMSC is the most prevalent type of SC in the United States. BCC accounts for 75% of all NMSC and is widely regarded as the greatest prevalent type of NMSC [55].

BCC and SCCs of the epidermis are cancers that originate from keratinocytes. These tumors exhibit significant variances in their diagnostic and histological characteristics, and are probable different in their underlying causes as well. BCCs are generally characterized by their slow growth, tendency to invade nearby tissues, and infrequent occurrence of metastasis. On the contrary, SCCs are characterized by their rapid growth, tendency to invade nearby tissues, and capacity to spread to other parts of the body [56]. The molecular processes occurring in the development of BCC and SCC happen to be heterogeneous, and existing evidence suggests that it is a complex procedure that often involves alterations in the p53 gene triggered by UV radiation [57].

The presence of different polymorphisms of human papillomavirus DNA was recently identified in NMSC, although its exact contribution to the development of NMSC is not well understood. Cutaneous HPV varieties, specifically those linked with EV, were found in 30 in excess of 80% of NMSC and their initial conditions [58]. Several investigations indicate a greater frequency of HPV in lesions observed in patients with weakened immune systems. Cancer-causing dangerous HPV (HR-HPV) varieties, including HPV16, are involved in 2-50% of NMSC along with SCC in situ, such as Bowen's disease. These HPV types are known to be directly associated with acquiring anogenital malignancies as well as certain head and neck malignancies. The available information regarding the activity of active viral oncogenes and the variation in the incidence of high-risk HR-HPV between individuals with weakened immune systems and those with normal immune function are not definitive [59].

Chronic HR-HPV transmissions can cause the conversion of nasal squamous epithelium cells into malignancies by deactivating the p53 and pRB proteins after the viral cancer genes E6 and E7 are activated. The transcription of dangerous human papillomavirus oncogenes in vaginal squamous mucosa is followed by significant as well as widespread amplification of the intracellular cyclin-dependent kinase preventing p16INK4a, which is observed in the nucleus and/or cytoplasm. However, in vaginal epithelium that is temporarily contaminated with high-risk human

papillomavirus (HR-HPV), where the production of HPV oncogenes is minimal, there is no observable widespread activity in p16INK4a [60].

Association of p53, HPV and Skin Cancer

The p53 gene functions as a promoter regulator, overseeing the regulation of the cell cycle and inhibiting the development of tumors. The detection of p53 immunostaining in premalignant and cancerous skin wounds of organ transplantation victims, as well as in individuals with a healthy immune system, suggests that the p53 protein exerts a substantial impact on the progression of skin carcinoma. The E6 protein of carcinogenic strains of HPV plays a vital role in the development of tumors by deactivating the tumor suppressor gene p53 [61]. An investigation has demonstrated that the Arginine variant at this codon is more susceptible to degradation. Although a thorough examination was carried out on participants who underwent organ graft, it was demonstrated that the presence of the p53 did not increase the susceptibility of individuals to developing skin tumors after renal graft [62]. Research has shown that the E6 protein of EV-HPV type 8 does not form a compound with p53, based on this discovery. HPVs that affect the skin infiltrate and persist as distinct genetic entities within the basal keratinocytes, namely in the area surrounding hair follicles. These follicles act as a reservoir of stem cells that contain unique attributes. Mice carrying transgenic genes encoding the whole initial domain of HPV8 undergo cellular activation and proliferation during the process of damage healing and the development of skin tumors [63, 64].

Mucosal HPVs mainly affect the p53 and pRb proteins, resulting in the alteration of the host cell and the commencement of uncontrolled cell proliferation. This transition is achieved by interfering with multiple cellular functions, such as cell cycle arrest, metabolism, apoptosis, and communication with the defense system [65]. Contrary to alpha-type HPVs, cutaneous papillomaviruses utilize distinct mechanisms to interfere with their host cells. Instead of employing E6AP to facilitate the degradation of p53, the E6 protein found in most HPV genera, such as HPV1 and HPV8, interacts with MAML1 and inhibits NOTCH signaling. This trait is also seen in animal papillomaviruses, such as BPV1, MmuPV1, and MnPV. MAML1, together with the histone acetyltransferases p300 and CREBBP, can form a promoter component that enhances the activation of this channel [66]. NOTCH functions as both a tumour suppressor and a promoter of keratinocyte growth. Consequently, mutations in epidermal SCCs are frequently seen. The cell's uncontrolled growth and tumour development are facilitated when the mechanism is disrupted, either by genetic alterations or interference from HPV. HPV5 and HPV8 impair the maturation of recipient cells by breaking down p300 through E6, leading to a decrease in the synthesis of keratin 1, keratin 10, and involucrin [67].

Furthermore, the HPV38 E6 protein interacts with p300, preventing the acetylation of p53 and hindering p53-mediated cell death. HPV38 E6 can increase the synthesis of a shortened form of p73, which lacks a region responsible for activating gene transcription. ΔNp73 hinders the functioning of p53, which may disturb the process of apoptosis and the removal of damaged HPV-positive cells. Recent studies have shown that HPV8 E6 promotes the continued expansion of the host cell by inhibiting the CCAAT/enhancer-binding protein (C/EBPα) and decreasing the amounts of microRNA-203, which normally suppresses the formation of ΔNp63. This outcome is attained by directing attention towards p300 [68, 69]. While p63 serves as the main regulator of epidermal stemness, it possesses the capability to induce cell cycle arrest and apoptosis, comparable to p53 and p73. However, ΔNp63 can act in a dominant-negative manner and support the proliferation of cells. Specific beta-HPVs specifically affect important points in the cellular network that control biological differentiation, senescence, and apoptosis. This process sufficiently explains the viruses' capacity to stimulate the formation of immature tissues. The occurrence of non-melanoma skin cancer is greatly influenced by the impact on tissue homeostasis, particularly when skin contaminated with HPV is frequently exposed to UV rays [70].

Under typical circumstances, exposure to UV radiation induces the stabilization and activation of p53, leading to a cessation of the cell cycle and the commencement of DNA repair processes. Nevertheless, in higher quantities of sunlight, it is prone to apoptosis. Impaired p53 function leads to a gradual accumulation of modified cells, hence promoting the advancement of NMSC. High-risk

epithelial types primarily target the p53 protein directly after DNA damage, while epidermal beta-HPVs affect other DDR proteins that are linked to p53. The HIPK2 protein plays a critical role in linking the ATM/ATR pathway to p53-induced apoptosis [71]. After being exposed to a significant amount of UV radiation, HIPK2 interacts with p53 and the CBP acetyltransferase. This interaction leads to HIPK2-mediated phosphorylation of p53 and CBP-mediated acetylation of p53. As a result, there is a strong activation of p53, which is accompanied by an increase in the expression of genes that are involved in programmed cell death. HPV23 E6 can inhibit the activation of p53 by HIPK2 following exposure to sunlight, as demonstrated in one of the most prevalent types of HPV found in the skin. Surprisingly, HIPK2 also controls the abundance of stem and progenitor cells in the skin, which act as the origin of epidermal HPVs. In addition, animals that do not have HIPK2 are more susceptible to developing SCCs. This aligns with the lower levels of HIPK2 expression observed in keratoacanthomas (KAs) and SCCs, as opposed to actinic keratoses (AK) [72]. In addition, beta-HPVs has the capacity to inhibit the elimination of pyrimidine dimers induced by UV radiation, as well as to selectively break down the pro-apoptotic protein Bak by proteolysis. However, the interference with the DDR and pro-apoptotic pathways can result in long-lasting effects on chromosomal instability and promote the accumulation of dysfunctional cells. Moreover, HPV8 E6 amplifies UV-triggered EGFR signaling, which causes a rise in keratinocyte hyperproliferation and skin inflammation, ultimately leading to the formation of SCC [73]. Furthermore, the E7 proteins of HPV5 and 8 alter the beta-catenin and zona occludens-1 anchor proteins, resulting in the disturbance of the attachment and tight junctions in the epithelial cells. Their restructuring disturbs the balance within cells and triggers epithelial-mesenchymal transition (EMT), suggesting a possible role in the development of NMSC. This is consistent with the process by which HPV8 E7 enhances the production of metalloproteases, which alter the external surroundings to facilitate the migration and infiltration of cells that are positive for HPV8. Furthermore, HPV8 E7 promotes the synthesis of fibronectin, an additional characteristic of EMT, by inducing a shift from E-cadherin to N-cadherin transcription in the upper layers of tissues in organotypic skin preparations. This change is considered a pivotal stage in the dissemination of cancer patients [74].

Various malignancies, including NMSC and carcinomas of the gastrointestinal tract, larynx, and cervix, are predominantly attributed to external factors, mainly viral agents. Multiple studies have investigated the role of HPV in the development of cervical cancers. Moreover, HPV has been associated with some lymphomas and esophageal malignancies, potentially playing a role in their development [75, 76]. Nevertheless, subsequent inquiries failed to confirm the presence of HPV or any other virus in these cancers. Based on the facts at hand, there exists a spectrum of strength in the association between viral infections and cancer in individuals with weakened immune systems. Nevertheless, laboratory experiments have demonstrated that the E6 and E7 proteins have an impact on the mitotic checkpoints of the cell cycle specifically during the G1 phase. Although the full extent of the effects of these early proteins is not yet understood, recent research has demonstrated that E6 and E7 proteins from high-risk HPV subtypes have significant interactions with the proteins p53 and pRb, which are crucial regulators of the cell cycle [77].

When HPV-infected modified squamous cells penetrate further levels and undertake EMT, it is probable that HPV replication, which heavily relies on cell differentiation, cannot be sustained. As a result, the existence of a virus is hardly longer required for the development of cancer, as the tumor develops diverse by gaining more abnormalities. Although mucosal and cutaneous HPVs possess distinct mechanisms of action, they both result in an identical end [78, 79]. Hence the instance of ovarian cancer, HPV becomes incorporated with the genetic of the target cell, while still maintaining the altered phenotype through continuous production of E6/E7. In contrast, cutaneous HPVs disrupt their host cell at the first stage of the complex mechanism of cancer development, ultimately resulting in an internal condition that inhibits the recurrence of episomal DNA. This could potentially elucidate the reason behind the absence or reduced presence of viral infections in SCCs in comparison to pre-malignant areas. Regardless, this situation is a "dead end" to both epithelial and cutaneous HPVs, as the favorable phase is disrupted and no new viral progenies ought to be generated [80]. The summary of involvement of HPV and its types with skin cancer are sum up in the table 1, as given below;

Table.1

Type of Virus	Resulted Cancer	References
HPV	Skin cancer	Bandolin *et al*., 2020; Smola, 2020; Chen *et al*., 2021
β-HPV	SCC	Accardi & Gheit, 2014; Genders *et al*., 2015; Tampa *et al*., 2020
HPV	BCC & NMSC	de Giorgi *et al*., 2012
cHPV	BCC	Iannacone *et al*., 2013
β-HPV	Skin cancer	Borgogna *et al*., 2018 Minoni *et al*., 2020;
HPV	NMSC	Harwood *et al*., 1998; Drvar *et al*., 2014; Arroyo Mühr *et al*., 2021
HPV	SCC	Eliezri *et al*., 1990; Gillison *et al*., 2015; Aggarwal *et al*., 2020; Paradisi *et al*., 2020; Rollison *et al*., 2021; Barillari *et al*., 2021; Lozar *et al*., 2023; Tan *et al*., 2023;
β-HPV	NMSC	Viarisio *et al*., 2018; Kricker *et al*., 2022

HPV and Melanoma

Skin cancer that is most fatal is melanoma and main factors responsible for the development of cutaneous melanoma are UV exposure and HPV. It's true that preventative efforts against sun exposure and the usage of different sunblock creams may have had some beneficial impacts. UV exposure, particularly UVB rays, has been linked to the formation of some mutations in vitro from a cellular and molecular perspective. Still, these patterns of mutation are not constant. However, very few of these mutations were linked to the control of the cell cycle, particularly in melanoma where the p53 regulatory protein is involved. These findings imply that other substances could have a direct or indirect role in the onset and spread of melanoma [81].

The functions of p53, a cancer inhibitor protein engaged in the restoration of UV-type DNA breaks, are influenced by E6 proteins. The tumor suppressor protein p53 is broken down more easily by the E6 protein. This leads to a substantial decrease of the p53 binding to DNA ability and interferes with the body's ability to react to harm to DNA [82]. E7 protein predominantly modifies the activity of retinoblastoma proteins throughout the cell cycle's G1/S phase. The dysregulation of cyclin E is linked to the impairment of the G1/S transformation in human cells carrying HPV type 16 E7. The early induction of cyclin E-associated kinase expression shortens the transit through G1, which is one of the many components of the cell cycle machinery that is significantly impacted by the E7 protein. In addition to preventing the G1/S cell cycle from progressing normally, this also releases the transcription factor E2F [83, 84]. Both of these proteins' comparable actions on melanocytes in vitro result in the immortalization of these cells as well as normal human keratinocytes. Lastly, new data show that some melanoma tumor biopsy samples include HPV. These findings, along with our previous discovery of Papillomavirus in cells of skin cancer isolated from tissue samples in vitro, imply that HPV could be involved in the onset and spread of melanoma [85].

Another investigation was to ensure if HPV was detected in tissue biopsy samples from melanoma cases, and if so, whether HPV was connected to both the clinical prognosis and prolonged melanoma growth in vitro cell cultures. According to the results, HPV was detected in 58% of the tissue samples taken for skin cancer that were analyzed, it was connected to the ongoing in vitro proliferation of melanoma cells, and it was linked to a worse outcome for melanoma patients with stages 3 and 4 of

the AJCC. Viral oncoproteins may be detected in biopsy specimens using a variety of techniques, such as in situ hybridization, polymerase chain reaction (PCR), and immunohistochemistry. Skin malignancies other than melanoma and cervical carcinoma samples have been subjected to PCR detection of several HPV subtypes. However, as demonstrated by the clinical PCR diagnosis of Mycobacterium TB, a considerable proportion of false-positive findings may arise due to the sensitivity of this approach. Concerns including controlling amplification products contamination, preparing samples to prevent antagonists, and translating positive results are still issues that need to be resolved when using PCR technologies for clinical diagnosis. An immunohistochemical method using a particular polyclonal antibody that identified the majority of HPV types was used for the current investigation [86]. Furthermore, because of the unequal skin cancer cell dissemination in the sample tissues, it was feasible to identify HPV and melanoma cells simultaneously by labelling consecutive sections. Using the samples, HPV was stained for the course of the trials in the positive (condyloma biopsy) and negative (normal skin biopsy) controls. This implies that the melanoma biopsy specimens' HPV may have been detected by the immunostaining method employed here. It is being investigated if in situ hybridization methods will validate this conclusion [87].

As previously said, the fact that HPV is found in some biopsy specimens' melanoma cells suggests unequivocally that HPV is linked to some melanomas. In recent clinical situations, two forms of HPV—HPV 16 and HPV 38—have been linked to melanoma. Furthermore, HPV 16 and HPV 35 have been detected in our lab's cell lines that were generated from biopsy specimens for melanoma. HPV has been connected to a number of nonmelanoma skin cancers, such as immunosuppressed people, cutaneous squamous cell tumors from renal allograft patients, and EV. It has been established that HPV infection is linked to the emergence and spread of invasive malignancies of the skin, head, and neck [88]. Furthermore, according to a recent research, HPV was frequently found in normal skin and was detected in over one-third of the skin biopsy specimens examined. Others, on the other hand, discovered that the DNA of individuals with cSCC did not include any HPV type 16 sequences. According to our observations, few of the normal skin sample in skin biopsies had HPV, as previously reported. In both healthy skin and skin lesions, many HPV kinds, including HPV 5, 16, 20, and 38, were discovered [89]. We are analyzing the HPV kinds found in our tissue specimens, particularly HPV 16, 18, 35, and 38. When melanoma biopsy specimens tested positive for HPV, five out of seven cell cultures that were separated developed in vitro. This discovery aligned with our earlier research on cell lines of melanoma obtained from recently harvested biopsies. Actually, out of the 22 melanoma cell cultures that were subjected to PCR analysis, HPV was found in 58% of them. The PCR findings were sequenced to identify HPV types 16 and 35. The effect of E6 and E7 proteins upon the cancer cell cycle may be related to the presence of HPV in the in vitro cultures of cells. In fact, the cells became immortalized when the E6 and E7 open reading frames of HPV type 16 were introduced into cultivated normal human melanocytes. To create a specific melanocyte cell line in vitro, these two proteins were all that were needed [90, 91].

The process underlying the alteration of the melanoma cell cycle are probably similar to those that have been thoroughly investigated in cervical cancer. Research has shown that the earliest HPV E6 and E7 proteins promote cell division by advancing up cyclins A and E. and by disrupting the functioning of p53 and Rb, two cell cycle regulators. The HPV-infected epithelial cells were significant aimed for the viral cancer-causing proteins E6 and E7, which are p53 and pRb products of tumor suppressor gene. Through the use of antisense RNA targeting E6/E7, HPV-positive cancer cells' selective E6/E7 downregulation was achieved, the crucial significance of these proteins was demonstrated [92]. Furthermore, the tp53, p16, and p21 genes showed little to no alterations in oral cancer lesions linked to HPV. Furthermore, 63% and 48% of NMSCs in renal transplant patients. There was no correlation seen in either study between the p53 mutation and HPV status as only two of the 25 cell lines examined have p53 mutations. This finding is consistent with earlier research showing a low frequency of p53 mutation in melanoma. It is unknown if further mutations contribute to the HPV-positive lesions [93].

The precise series of events that cause the cells to become immortal is still unclear, despite the fact that the early proteins E6 and E7 have been demonstrated to interact with other cell cycle proteins.

Furthermore, the possible mechanisms of HPV are still unknown and may involve UV radiation, similar to EV but different from anogenital and cervical malignancies. In actuality, a patient's chance of developing nonmelanoma skin cancer has been linked to both UV exposure and HPV infection. It is unclear if UV radiation alone or in combination with HPV infection is necessary for melanoma to begin and progress. Clinically speaking, our findings show that biopsy specimens that tested positive for HPV were linked to a worsening of the patient's prognosis. This implies that the occurrence of HPV may identify a kind of melanoma that is more likely to advance or recur. Despite the small number of biopsy specimens evaluated, the data strongly show a relationship between the occurrence of HPV in biopsy specimens taken from AJCC stage III and IV melanoma and a poor melanoma prognosis. The patient cohort under evaluation is bigger [94].

HPV and SCC

One of the root causes of SCC is recognized as HPV. HPV, a non-enveloped DNA virus, exclusively multiplies within keratinocytes following infection. HPV is believed to invade the body through small injuries in the outer layer of the skin or protective tissues. It attaches to and enters cells by interacting with certain substances on the outside of host tissue, such as glycosaminoglycans, proteoglycans, and viral capsid proteins. Although uncommon, there is evidence demonstrating that certain high-risk HPV variants may incorporate their DNA into the DNA of their hosts. The a, b, and g groups contain the largest of the over 100 different HPV strains. A-HPV variants essentially infection epithelial epithelium, such as the cervix and oral cavity, while b and g-HPV types predominantly invade epidermal epithelium. Tumor formation is induced by b-HPVs involving the suppression of programmed cell death and disruption of DNA healing processes by viral E6 proteins. Furthermore, they promote aggressive growth by disrupting the normal cell cycle of the host through viral E7 proteins [95].

Skin malignancies are distinguished into cutaneous, mucosal, and EV. EV, an uncommon cutaneous condition, greatly enhances the probability of cutaneous HPV infections and subsequent skin cancers. The physical appearance of HPV illness is determined by the viral genotype, ecological tumors, and the immunological condition of the individual. An investigation has found that a 34-year-old lady developed a SCC in situ on her left palmar hand, which was associated with HPV. Furthermore, she had no documented ecological hazards, including interacting with children, immunodeficiency, or EV, and she possessed no previous medical record of Verruca vulgaris. To our knowledge, there exists only previously reported case of cSCC in a child of such a young age who did not exhibit any associated risk components, specifically related to HPV. Evidence keeps confirming that HPV has a carcinogenic effect on the formation of both neoplastic and premalignant skin cancers [96]. The detection of seropositive antibodies and viral DNA in cancer cells suggests a robust correlation between HPV infection and the development of cSCCs, however the exact core reason for this link remains unknown. Furthermore, certain investigations have shown that premalignant irregularities such as AK, have a higher prevalence of HPV compared to SCCs, BCCs, benign tumors, or healthy skin. This implies that HPV may have a more important role in the formation of malignancies than in the maintenance of malignancies [97]. The presence of a virus in a-HPV-associated carcinomas results in the production of the viral oncoprotein E7. This oncoprotein then disables the retinoblastoma protein (pRb), causing an increase in the expression of the tumor suppressor protein p16. The protein P16 is frequently utilized as an immunohistochemistry indicator to identify alpha-HPV) lesions in SCCs found in the anogenital and mucosal regions, owing to its well-established mechanism. A positive categorization is assigned to p16 staining patterns that display substantial "block-type" nuclear and cytoplasmic coloring. While p16 is commonly used as a marker for nasal SCCs linked to alpha-HPV, it is crucial to recognize that further research is needed to show a direct relationship between p16 gene expression and cutaneous SCCs connected with beta-HPV. Prior research has demonstrated that SCCs associated to HPV display intense marking when subjected to the P16 indicator [98]. Ki-67 is a valuable marker for measuring cellular proliferation. The protein Ki-67 is expressed in the nucleus during all stages of the cell cycle, except for the G0 phase. This protein serves as a marker for the advancement of rapidly dividing cancer cells during the cell cycle.

HPV-associated SCCs exhibit pathological characteristics such as complete disintegration across the skin tissue, which may also involve the follicular tissue [99].

The biopsy outcomes for the individual's tumor in our case description were consistent with SCC and the immunohistochemistry (IHC) analysis confirmed the detection of an HPV element through p16 labelling. The patient, on the other hand, did not exhibit any of the risk factors commonly associated with SCCIS caused by HPV, such as immunosuppression, old age, or previous exposure of EV. An individual diagnosed with EV possesses an exceptionally uncommon hereditary skin disorder that heightens their vulnerability to infections associated with HPV. The hallmarks of this condition consist of verrucae-like lesions that are distributed across sun-exposed areas of the body, such as the hands, feet, cheeks, and ears. These symptoms can manifest at any point between infants and puberty [100]. Approximately 30-60% of these abnormalities have the capacity to develop into cancerous growths after the age of 30, typically manifesting as SCCs. The individual, although falling within the appropriate lifespan, does not possess a familial background in EV. Furthermore, a study examining precancerous and invasive skin abnormalities found that EV-HPV-DNA was more frequently identified in actinic keratoses than in SCCs. Based on this study, EV-HPVs may have a distinct function in the initial phases of skin cancer development [101].

Another group of individuals who are at an elevated risk of developing SCCs are those with impaired immune systems. Studies have shown that the HPV virus can trigger reactions from the body's defensive cells and the production of antibodies. The T-cell activation is particularly important in protecting against HPV infection. Studies suggest that individuals who have genetic defects in the quantity and frequency of their T-cells, including Dock8 deficiency, are particularly susceptible to viral illnesses. This increased vulnerability can result in the development of surface cutaneous verrucae and SCCs [102]. Furthermore, studies have shown that persons with established or iatrogenic immune weaknesses, such as those who are HIV positive or have undergone an organ transplant, frequently develop cutaneous SCCs. Furthermore, these patients exhibit inadequate defenses mechanisms against HPV. It is uncertain if their impaired immune system or an underlying immunological defect is responsible for their susceptibility to SCCs. However, it is important to acknowledge the tendency of persons with weakened immune systems to develop HPV-related cutaneous SCCs due to the increased risk in these populations [103].

Organ transplant recipients frequently suffer from the co-occurrence of squamous cell carcinoma and viral warts. Moreover, HPV DNA is frequently found in non-melanoma skin cancers. This indicates that both viruses could contribute to the onset of skin cancer. After the procedure, nearly all people will definitely acquire warts at some point [104]. Clearly, there exist multiple discrete variants of HPV. The following EV-associated HPV methods were enlisted: HPV5, 8, 12, 14, 19, 20, 21, 25, 36, and 47. These HPV forms have been linked to harmless, pre-cancerous, and carcinoma skin illnesses in individuals who have undergone organ transplantation. EV-HPV types are the most common forms of viruses found in all sorts of infections. A single site can contain various kinds of HPV. Organ transplant patients often have a single skin diagnostic sample that contains many types of HPV [34]. PCR techniques are commonly employed for the identification of certain subgroups of surface HPV strains that are linked to hereditary factors. The groupings consist of two categories of kinds of HPV that do not affect the skin, and three subcategories of HPV categories related with EV. Conducting direct DNA sequencing of the PCR output enables precise identification of HPV genetic variants, even in situations when multiple diseases are widespread. The prevalence of EV-associated HPV along with additional epidermis HPV varieties is similar in biopsy specimens obtained from AK 68%, SCC 78%, and hyperkeratotic papilloma 78%. The occurrence of this phenomena is less frequent in specimens collected from normal skin (32%), non-cancerous skin diseases (39%), as well as basal cell malignancies (36%). In a separate investigation, similar frequencies of incidence were observed, with HPV DNA being discovered in 88% of pre-cancerous wounds and 84% of squamous tumors. However, it is worth noting that the frequency of basal cell malignancy remained significantly increased at 75% throughout this investigation [105].

Exposure to UVR is a possible risk factor that could have contributed to the patient's cSCC progression. It is yet unclear how UVR and the development of cSCC are related. Research has

indicated that those having a past history of excruciating sunburns are more susceptible to HPV-related colorectal cancers. The current theory explaining this tendency is that UV radiation suppresses local cell-mediated defenses, leading to localized immunosuppression and favorable circumstances for HPV infection. As comparison to their non-irradiated counterparts, patients with psoriasis who received psoralen-UVA photochemotherapy also showed an elevated risk of HPV susceptibility. This provided more support for the theory that UV exposure might contribute to the growth of HPV infections. The risk of cSCCs often increases with age because exposure to ultraviolet radiation has an impact on the occurrence of cancer of the skin [106]. According to a thorough community-based investigation of non-genital SCCIS instances in a group of Europeans, immunocompetent people typically experience the beginning of SCCIS 73 years later, whereas immunocompromised patients experience it 63.5 years later. It's critical to investigate HPV as a putative trigger in SCC carcinogenesis since it raises the prospect of developing cutting-edge treatments and prophylactics for HPV-positive individuals. There are HPV vaccinations available currently that help prevent cervical cancer, Nevertheless, these only deal with 9 of the several HPV variants. Furthermore, active HPV infections are not completely eradicated by existing treatment approaches. Future treatments should make it possible to eradicate the virus and develop vaccinations that prevent additional HPV-induced malignancies, such as skin cancer. This may result in the lesions being completely cleared and recurrences being prevented [107].

This is a unique case of a relatively safe patient whose left the palmar region of hand developed an HPV-associated SCC without any risk indicators. Her age of 34 was considerably younger than the average age at which SCC develops, and she had no prior history of EV or immunosuppression. Based on these data, we postulate that the co-carcinogenic outcomes of ultraviolet radiation contact, regional suppression of immunity, and HPV infection. It is widely acknowledged that patients receiving long-term PUVA treatment have a higher chance of developing skin SCC. There is some evidence to suggest that adding methotrexate to individuals receiving long-term PUVA therapy increases their chance of developing SCC and maybe even moving on to metastatic SCC. In 75% of SCC, EV-HPV DNA, including HPV5, has been found [108].

The emergence of skin cancer other than NMSC in people with compromised immune systems, such as organ transplant recipients (OTRs), may be influenced by etiological agents referred to as beta HPV types. Compared to the general population, recipients of transplants of solid organs have a much greater prevalence of NMSC, especially for those suffering from cSCC, and additionally have a higher chance of getting warts caused by viruses. Keratinocyte carcinomas are more common in immunocompromised people, which may indicate a viral etiology. Immunocompromised individuals have a far greater chance of developing NMSC especially cSCC than normal people do, according to a comparison with general population rates. Within a 24-month period, skin cancer strikes two thirds of solid organ transplant patients. Within the next five years, two thirds of patients will acquire a second cSCC, as the cumulative incidence of cSCC rises gradually. 90% of patients will have viral warts 15 years after transplant, and nearly half (40%) will have acquired some kind of cSCC. Nonetheless, the risk varies depending on the kind of transplant, being progressively higher for the liver, kidney, lung, and heart. Finally, a viral origin is suggested by the increased incidence of keratinocyte malignancies in people with compromised immune systems [109].

Patients who have had transplants may develop cases of cSCC that resemble viral warts in both morphology and clinical features caused by HPV. Viral warts and cSCC typically coexist, which implies that these individuals may develop permanent viral warts. More significantly, transplant patients with actinic keratosis and cSCC had significantly greater β-HPV DNA frequency than the general population. While it is proven that β-HPV has a role in the etiology of cSCC in individuals with EV (and likely also in immunocompromised people), the role of β-HPV in the development of NMSC among the broader populace remains controversial. While the genomes of certain β-HPV kinds are often identified in NMSC instances in otherwise healthy persons, they are often present in premalignant lesions and even in skin that is in good condition [110]. However, compared to normal people, patients with a hi in skin lesions and even cancerous lesions story of cSCC had a higher chance of testing positive for β-HPV infection, according to epidemiological research. Contrary to

what happens with α-HPV, AK had a greater incidence of β-HPV than cSCC, which implies that β-HPV may have a role in the early stages of tumorigenesis. Furthermore, HPV has not been detected in cSCC by current sequencing studies, which is in contrast to findings in cervical cancer. Proof that HPV is the primary cause of skin cancer may be found in an experiment of genetically engineered mice. Skin cancer develops spontaneously in mice that produce the HPV8 area concurrently regulated by the human keratin-14 promoter; STAT3 appears to be involved in this process, and UV light speeds it up. A meta-analysis suggests that β-HPV infection is a potential risk factor for SCC onset among healthy persons, however it is still unclear how exactly β-HPV contributes to the emergence of cSCC in people in general. This relationship, namely with HPV17, HPV20, and HPV38, but also with HPV5 and HPV8, which are associated with cSCC in patients with EV, has been shown by subgroup research [111].

Treatment of HPV in SC

The use of a preventative vaccination that stops tumor growth is the best evidence supporting a virus's etiological role in the development of cancer. Currently authorized for preventing the development of anogenital tumors are three vaccines against HPV that are based on virus-like particles (VLPs) produced from L1, the major papillomavirus virion protein. Their targeting varies depending on whether it is two, four, or nine mucosal HPV types. Although they are very efficient, they have drawbacks that need the creation of second-generation immunological that are widely protective [112]. The majority of the mechanistic investigations demonstrated that the main mediators of the evoked response are vaccine-induced neutralizing antibodies, which provide immunity by preventing a future infection by the targeted HPV strains. At most, these vaccines target the highly susceptible types of HPV that cause 90% of cancer of the cervical cavity cases; they lack the ability to attack any epidermal variations since the immune system's reaction to these vaccinations has been shown to be largely type-specific and there is minimal cross-reactivity across other HPV types [113]. In fact, over forty HPV types are potentially targets for a vaccine aimed at preventing human diseases: mucosal high-risk HPVs implicated in the pathogenesis of cervical and other cancers are particularly burdensome in children and immunocompromised patients. It seems sense for second-generation vaccine research to aim for a preventive HPV vaccination that is broadly protective, considering the potential advantages of addressing so many distinct kinds of HPV [8].

Within this particular case, a significant cross-neutralizing domain is identified in a specific area of the principal immunogen for second-generation vaccinations is the minor capsid protein of the HPV which is also referred to as L2. The objective of developing an L2-based vaccination is to provide a single- or oligo-valent antigen that offers a significantly broader spectrum of protection against sexually transmission and cutaneous HPVs compared to current formulations. Due to the significantly lower antibody levels generated by L2-derived linear peptides compared to those produced by L1 VLP vaccines, various methods have been experimented with to immune responses. Effective responses included conjugation of a T-helper epitope and a TLR ligand, formation of L2 concatemers, display on phages or adeno-associated viruses, chimeric HPV L2 peptide/L1-VLPs, incorporation into the active site of a protein, or lipidation and fusion to an FcγR-targeting scaffold. These strategies have generated neutralizing antibodies that can effectively neutralize a wide range of targets, thus demonstrating the feasibility of employing this method [114].

Different vaccine compositions such as L1 or L2-based have shown to produce antibodies that directly target or cross-protect against PV cutaneous variants. Specifically, two investigations have demonstrated that these immunizations can successfully shield preclinical animals from skin lesions. A vaccination targeting epidermal papillomavirus based on vectors was found to be able to prevent the development of spontaneous skin tumors in both immunocompromised and healthy persons [115]. As previously noted, MnPV-positive shares many traits with human conditions and cutaneous HPVs, including as early-life, natural, and chronic infection. When evaluating a VLP-based vaccine's effectiveness against infections that have already occurred or have just started, it may be possible to see a sustained response, which is marked by the production of neutralizing antibodies that provide protection against skin tumors that are benign and malignant, even in immunocompromised animals

[116]. Surprisingly, this study also showed that protection keeps the skin's viral load low, which prevents the virus from spreading. Furthermore, even in those who were previously afflicted at the time of immunization, it successfully inhibits the development of tumors. These results demonstrate that VLPs may effectively elicit an immunological reaction in the skin regardless of the infection status at the time of vaccination, especially in cases of immunosuppression. In the future, this might pave the way for the clinical development of a vaccination to prevent cutaneous HPV-induced tumors and therefore prevent SCCs, especially in OTRs [117].

The use of DNA vaccinations in cases of cutaneous HPV infection has also been investigated. According to a recent study, a vaccine containing HPV8 E6 DNA can cause a particular cellular response in around half of the vaccinated animals and, in those that established HPV8-E6-specific T cell immunity, partially inhibit the production of papillomas. With respect to L2 vaccinations, a basic HPV16-L2 DNA vaccine did not elicit neutralizing antibodies and, hence, did not have the potential for cross-reactivity [118]. On the other hand, a different vaccination that included HPV16-L2/E6/E7 fused to human calreticulin (hCRT) in an attempt to improve MHC class, presentation produced both L2-specific neutralizing antibodies and T-cell responses specific to E6/E7, indicating promise for both prophylaxis and therapy. In an in vivo neutralization study, hCRT-E6E7L2 provided partial protection; however, its cross-neutralization activity has not yet been documented. Moreover, hCRT-E6E7L2 immunization preserved cellular immunological responsiveness in CD4+ T cell-depleted mice when tested in an immunosuppressed environment, but it was unable to elicit a humoral response [119].

It is now possible to do vaccination research on this animal system as well, because to recent developments in the MmuPV1 model. An hCRT-MmuPV1E6E7L2 DNA vaccination produced potent anti-L2 antibodies as well as mE6 and mE7 CD8+ T cell responses. In addition to the vaccine-induced antibody titers, a robust anti-L1 response was also observed in the animals, regardless of their papilloma status. This was probably caused by the inoculum that was used for the experimental infection [120]. Surprisingly, after two months of therapy, persistent papillomas vanished and the virus was eliminated. Since the anti-L2 reaction coincides with the E6 and E7 responses, the significance of neutralizing anti-L2 antibodies cannot be separated due to the vaccine's design. Hence, in order to determine the efficacy of pure L2 vaccinations in lowering skin malignancies, a thorough examination using a preclinical paradigm remains necessary. Considering the established fact that L2 reactions are inferior to L1 reactions, it is essential to investigate if L2 vaccination can produce sufficient neutralizing antibodies to effectively prevent cancer development, particularly against non-cognate HPV strains. Animals that have been vaccinated show complete shielding against disease, even when blood samples show antibody levels that are insufficient to be detected by laboratory techniques that measure neutralization. This suggests that even quite small amounts of antibodies are sufficient to provide immunization [121].

HPV and Merkel Cell Carcinoma

The Merkel Cells linked to nerve terminals were discovered in the basal layer of the skin, in the follicles of hair, on some surfaces of the mucous membrane, and in touch-sensitive regions. Because of this, their purpose was originally believed to be connected to touch perception [122]. The word trabecular carcinoma originated from a description of a tumor made up of tiny, extremely basophilic, polygon-shaped cells arranged as trabeculae by Toker in 1972. Merkel cells were the cellular source of trabecular cancer because of the neurosecretory granules present in the inner structure. Prior to 1990, Merkel cell carcinoma (MCC) was an uncommon diagnosis; however, with the CK20 antibody development in the early 1990s, MCC diagnoses increased. Neuron-specific enolase, T antigen, synaptophysin, and CK20 are all positive in the cells [123].

The discovery of cytokeratin 20 (CK20) as an antibody in the early 1990s made MCC diagnosis easier and more accurate. This also led to a considerable rise in reported incidence of MCC, which helps to explain why the rate has quadrupled in the previous 20 years. There was very few trustworthy research about the effects of this type of NMSC prior to the 2000s. The three main risk factors for developing MCC are immunocompromised state, advanced age, and UV radiation exposure. Considering the

prevalence of older citizens in our culture who were subjected to ultraviolet (UV) rays, these warning signs categories it as a form of carcinoma that requires more examination. Merkel cell polyomavirus (MCPyV) is a member of the polyomavirus family [124]. This is evident in its double-stranded DNA and compact circular genome. Its length is 5389 base pairs, and its early- and late-coding portions are divided by a non-encoding regulatory domain comprising the viral replication site. The initial genes, known as the big and small T antigens, are synthesized by the T antigen locus. These genes frequently participate in the replication of the viral genome and are synthesized immediately upon infection [125]. The endogenous region is transcriptionally active after DNA replication to produce gene expressions essential for retaining the crystalline integrity of the viral capsid and assisting in producing progenitor virion in the final phase of transmission. The MCPyV genome has characteristics with other human polyomaviruses, such as competing early and late gene sections and a conserved replication origin [126].

The origin-binding domain (OBD), the replication-starting component, is known to be exclusively bound by pentanucleotide consensus sequences seen in polyomavirus replication origins. This helps LT proteins assemble on DNA. Polyomaviruses often attack protein molecules responsible for tumor repression and cell division control with their initial products of gene. The early area can also be referred to as the T antigen site because these products of genes are known as tumor antigens, or T antigens. Important tasks are also carried out by the polyomavirus T antigens at the start of viral DNA production [127]. Three T antigens are expressed in the MCPyV early region: LT, sT, and 57kT. While the brief amino-terminus of all three is similar, their individual characteristics are ultimately determined by alternative splicing that occurs downstream of the first exon. The MCPyV genome's late region has open reading frames for VP1, VP2, and VP3. The primary viral oncoprotein is MCPyV LT, whereas sT has an auxiliary function during transformation [128].

An uncommon and frequently deadly neuroendocrine skin cancer is called MCC. Its frequency in the United States is about 1500 cases annually, comparable to that of dermatofibrosarcoma protuberans and cutaneous T cell lymphoma. It makes up less than 1% of all occurrences of skin cancer, and is the third most prevalent cause of skin cancer-related deaths. During the three decades from 1981 to 2011, the incidence of this disease grew steadily in the United States. The elderly and individuals with immunocompromised conditions—whether being infected with HIV and transplantation of organs, or hematological diseases—are among the group at risk. With its peak incidence occurring during the ages of seven and eight decades, this malignancy is more frequent in older people. Merely Five percent of patients are under 50. of age at diagnosis, with an average age of 75. It has been shown that UV light and polyomavirus have a significant role in the carcinogenesis of MCC [129].

An acronym can be used to represent the most prevalent clinical characteristics of MCC: AEIOU: immunosuppressive, more than 50 years old, asymptomatic/lack of discomfort, fast growing, and located on a UV-exposed site. The majority of primary MCCs (89%) display three or more of these traits. Immunocompromised individuals, such as those with chronic lymphocytic leukemia and recipients of solid organ transplants, have shown a marked rise in the prevalence of MCC. MCC mostly affects older people., with beginning ages averaging 74 and 76 years for men and women, respectively [130]. It nearly mainly affects people who are Caucasian and develops in areas where UV radiation is present. As a matter of fact, the disease's prevalence and closeness to the equator are associated. Interestingly, it has been shown that the MCC p53 gene has undergone some UV-induced mutations, and that Merkel cells are more common in sun-exposed skin areas than in non-exposed skin areas. All things considered, ultraviolet (UV) rays and suppressed immunity appear to have a role in the pathophysiology of MCC. With a chance of surviving of five years lower than any other type of skin cancer, MCC was once thought to have a bad prognosis [131].

Compared to malignant melanoma, this malignancy has a greater five-year relative death rate (46% vs. 15%), and patients that do not exhibit clinical signs of nodal illness have a 32% likelihood of microscopic nodal involvement. Broadly speaking, 6–12% of individuals show distant metastases, while up to 37% of patients begin with lymph node metastases [132]. The dearth of prospective treatment trials and the dearth of centers with expertise or a special interest in MCC have made care of the illness difficult. As a result, nothing is known about the true effect of the incidence and

mortality linked to this particular kind of skin cancer. The preferred course of therapy for localized Merkel cell cancer is surgery. Although 1-2 cm margins are advised for functional reasons, the suggested resection margins for MCC have not been evaluated. Adjuvant radiation is quite likely to improve survival, as evidenced by a number of retrospective investigations, and is thus advised. Adjuvant radiation has shown promise in managing MCC locally, even in cases where the main tumor's excision had positive margins. As a matter of fact, it appears that the features of the surgical margin have little bearing on the pace at which the illness returns following radiation therapy. In almost 25% of people with MCC, occult lymph node disease is prevalent [133].
Although no studies have shown that surgical and rehabilitative removal of the lymph nodes improves long-term survival chances, it is advised if micro metastases are found. Avelumab, a phase 2 research using anti-PD-L1 an antibody that is mono demonstrated a 32% response rate in patients with metastatic MCC who had not responded to traditional chemotherapy; at a 10-month follow-up, 82% of those patients were still responding [134].

Psoriasis and HPV

EV-HPV DNA, specifically types 5, 36, and 38, has been detected in as many as 90% of the skin blisters and scratches of individuals with psoriasis. The viral DNA was detected at a frequency of approximately 1 in 20,000 cells, or an average of around 1,000 cells, during the determination of the virus load. The presence of antibodies against HPV types 5 and 8 VLPs in psoriasis subjects indicates a higher occurrence of effective contamination in contrast to normal individuals [135]. Psoralen is administered as a component of photochemotherapy for psoriasis, which is subsequently accompanied by UVA radiation (PUVA). There is no disparity in the general occurrence of HPV DNA between those who undergo PUVA treatment and those who do not [136]. Nevertheless, after photochemotherapy, a greater number of HPV strains are frequently detected. One study provides indications that persons who had been subjected to elevated levels of PUVA had a greater likelihood of detecting HPV types 5 and 8 [137].
The replication of latently persistent EV-HPV will be enhanced by the significant expansion of keratinocytes in psoriasis, leading to a higher rate of viral DNA identification and the activation of antibody responses. Additionally, situations involving rapid growth of keratinocytes, such as the process of skin healing in persons with severe burns or autoimmune bullous illnesses, result in the production of antibodies against HPV5. The relationship between HPV and these illnesses, whether as a cause or a consequence, remains uncertain. There is speculation that HPV proteins serve as "autoantigens" in the development of psoriasis through autoimmune mechanisms. Furthermore, HPV may facilitate the process of epithelial regeneration and maybe assist the patient in repairing the epidermis [138].

Conclusion

Human papillomavirus has been the major risk factor for skin cancer and its types according to the recent data. There are strong evidences for the association of human papillomavirus with squamous cell carcinoma, basal cell carcinoma and melanoma. HPV has various potential pathways to disturb normal cell cycle and trigger mutated keratinocytes for skin malignancies. The effect of HPV regarding tumorigenesis and disturbing p53 and pRb genes takes place through its E6 and E7 genes with combined influence through ultraviolet radiations. Moreover, HPV has proven to have a strong relationship with the Merkel cell carcinoma and psoriasis. These oncogenic proteins E6 and E7 can be used as a target point for therapeutic purpose of skin cancer. In the light of these information, well-developed prevention from HPV and treatment of skin cancer along with its types are the need of hour.

Conflict of interest statement:

The author declares that they have no conflict of interests.

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