

# Clinical Medicine Insights: Oncology



REVIEW

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## The Combined Influence of Oral Contraceptives and Human Papillomavirus Virus on Cutaneous Squamous Cell Carcinoma

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**Abstract:** The vast majority of cutaneous squamous cell carcinoma (CSCC) will occur in those with fair complexion, tendency to burn, and high ultraviolet radiation (UVR) exposure. Organ transplant recipients also are an important population at great risk for CSCC. An association has been reported between oral contraceptive (OC) use, human papillomavirus virus (HPV) and cervical cancer, and there could be a similar association for CSCC. The cutaneous HPV  $\beta$ -E6 protein, a close cousin of the transformative E6 protein underlying anogenital cancers, has been shown to inhibit apoptosis in response to UVR damage and stimulate morphologic transformation in rodent fibroblast cell lines. Furthermore, OC use has been shown to enhance HPV transcription and may contribute to CSCC risk through this pathway.

**Keywords:** cutaneous squamous cell carcinoma, human papillomavirus virus, oral contraceptives

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## 1. Introduction

Cutaneous squamous cell carcinoma (CSCC) is the second most common malignancy among Caucasians in the United States (US).<sup>1,2</sup> Often locally aggressive and resulting in substantial morbidity, this cancer rarely spreads distally.<sup>3,4</sup> However, while the overall 5-year metastatic rate is  $\leq 5\%$ , lesions of the lip and ear are particularly aggressive, with metastasis rates approaching 20%.<sup>5-7</sup>

CSCC occurs more commonly among iatrogenically immunosuppressed patients, and the potential for metastasis also is greater in this population.<sup>7-12</sup> In immunosuppressed organ transplant recipients (OTR), lesions occur primarily in chronically sun-exposed skin,<sup>13,14</sup> typically are histologically deeper at time of diagnosis,<sup>13</sup> increase in incidence with duration of immunosuppressive therapy,<sup>15</sup> and are characterized by a 4:1 reversed squamous-to-basal cell type (ie, basal cell skin cancer is the predominate type in immunocompetent patients).<sup>16</sup> Human papillomavirus virus (HPV) DNA is detected in approximately 75% of CSCCs from OTRs, compared with 47% in non-immunosuppressed patients,<sup>17</sup> and is thought to be a factor in the etiology of these cancers.<sup>6</sup> Also, high metastatic rates have been reported for radiation-induced CSCCs of the face and neck<sup>18</sup> and for CSCCs arising in patients infected with human immunodeficiency virus (HIV),<sup>19,20</sup> rates are comparable to those of squamous cell carcinoma (SCC) of the cervical and anal tracts in immunosuppressed patients.<sup>21</sup>

CSCC is observed more frequently in Caucasians than African-Americans (AA), Asians, or Hispanics.<sup>22</sup> Among AA, CSCCs are commonly located on the lower extremities and have a reversed squamous cell-to-basal cell ratio resembling that of immunosuppressed OTRs.<sup>22-26</sup> The lesions often arise from scars, burns, and ulcers and tend to be histologically invasive.<sup>24,26-29</sup> Approximately 29% of AA with CSCC develop regional lymph node metastasis and succumb to the disease.<sup>27</sup> CSCC is paradoxically rare in AA and Asian OTRs,<sup>15,30</sup> possibly reflecting differences in the ethnic distribution of HLA B27 and HLA A11,<sup>31-33</sup> the former predisposing and the latter conferring resistance to skin tumors.<sup>34</sup>

The associations of CSCC with ultraviolet radiation (UVR)<sup>35,36</sup> and innate pigmetary factors such as fair complexion (eg, propensity to burn on initial

exposure; inability to tan on repeated exposure),<sup>37-41</sup> light-colored eyes, and red hair<sup>37,38,40-44</sup> are well established. Chronic exposure to UVR is known to induce immunosuppression<sup>45-48</sup> and to promote skin carcinogenesis.<sup>49-53</sup> Sunlight does not play a significant etiologic role in CSCC among African-Americans, since most lesions present on covered areas.<sup>24,27,54-56</sup> The effect of cumulative lifetime sun exposure on CSCC is greatly diminished after adjustment for pigmentary factors.<sup>37</sup>

The greater frequency of CSCC than basal cell skin cancer (BSCC) on the upper limbs suggests that UVR exposure alone does not fully explain risk for CSCC.<sup>57</sup> This also is indicated by the substantially lower incidence of CSCC among Hawaiian Caucasians than Australian Caucasians.<sup>58</sup> Other factors associated with CSCC include ionizing radiation/radon,<sup>18,59-67</sup> certain chemical compounds,<sup>22,68,69</sup> iatrogenic immunosuppression,<sup>11,70,71</sup> physical trauma (burns and scars),<sup>68,72,73</sup> human papillomavirus virus,<sup>17,74-78</sup> higher education,<sup>42,59,79,80</sup> and genetic predisposition (xeroderma pigmentosa, epidermoplasia verruciformis).<sup>68</sup> Latent intervals of 40 or more years suggest that the risk of cancer in irradiated skin persists for the life of the person, and raise the possibility of long latencies for other short-term exposures in the etiology of CSCC.<sup>18</sup>

An increase in the incidence of CSCC over time has been reported in several longitudinal studies.<sup>81-87</sup> The increase may reflect lifestyle changes such as increased voluntary exposure to UVR (eg, frequent use of tanning salons, increased outdoor recreational activity, tendency to wear less sun protective clothing, mid-winter vacations in sunny locations), increased sexual activity resulting in exposure to HPV, and/or greater life expectancy. The depletion of the ozone-layer also may be a contributing factor.<sup>88-90</sup> A 1% percent reduction in stratospheric ozone is estimated to increase the incidence of nonmelanoma skin cancer (NMSC) between 3% and 6%.<sup>88,91</sup>

Understanding exposures that predispose individuals to CSCC is especially important since individuals with this cancer may be more likely to develop and die from certain secondary malignancies.<sup>92-116</sup> In the paper, we briefly examine the potential role of OC use on cancer risk in general and then specifically address the plausibility of OC use as a risk factor for CSCC, as suggested by recent epidemiologic studies.<sup>42,117</sup>





cancer cells.<sup>119–121</sup> Subcutaneous administration of oestradiol in mice increases the incidence of mammary, pituitary, uterine, cervical, vaginal, lymphoid, and testicular tumors.<sup>122</sup> In contrast, high doses of oestradiol significantly reduce ( $P < 0.05$ ) the incidence of cervical squamous cell carcinomas induced in mice with 3-methylcholanthrene (MCA).<sup>122</sup> The use of combined OCs (co-administration of an estrogen and a progestogen) has been classified as carcinogenic to humans by the International Agency for Research on Cancer (IARC).<sup>121</sup> However, the evidence linking OC use with cancer in humans is neither consistent nor definitive.<sup>121,123–125</sup> For example, OC use appears to promote cancers at some sites (eg, triple-negative breast cancer<sup>126</sup>), while affording protection at other sites (eg, endometrial cancer<sup>127</sup>).

### 3.1 Cutaneous squamous cell carcinoma

The epidemiology of CSCC has been difficult to study because few cancer registries record this cancer on a routine basis. Furthermore, CSCC and BCSC, which are biologically and histologically distinct cancers with different clinical characteristics, often are studied under the general heading of NMSC.

An analysis of self-reported skin cancers, excluding CM, in the Oxford Family Planning Association (Oxford-FRA) contraceptive study did not observe a greater risk for these cancers among OC users (ever used, RR = 0.9, 95% CI = 0.6–1.4; recently used, RR = 0.4, 95% CI = 0.1–1.2; used in past, RR = 1.0, 95% CI = 0.6–1.6) than hospitalized referents who had never used oral contraceptives.<sup>128</sup> However, the findings from this study are difficult to evaluate since cases were self-reported and the comparison group consisted of hospital clinic patients whose use of oral contraceptives may not have been representative of the population from which cases were selected.

Except for the above report which included both CSCCs and BCSCs, only two papers to date specifically have studied the association between OC use and CSCC (Table 1). A large population-based case-control study<sup>117</sup> found that OC users had a 1.6 adjusted OR for CSCC (95% CI = 1.0–2.5). ORs also were higher among women who last used OCs  $\geq 25$  years before diagnosis (OR = 2.1, 95% CI = 1.2–3.7), and within-group ORs increased with duration of use [OR for  $\leq 2$  years, 1.7 (95% CI = 0.9–3.5); OR for 3–6 years, 2.6 (95% CI = 1.0–6.5); OR for  $\geq 7$  years,

**Table 1.** Summary of studies on OC use and risk for CSCC.

Author, year published, study location	Study design	No. of cases	No. of referents	Main effect risk estimates (95% CI)	Comments
Applebaum et al, 2009, New Hampshire <sup>117</sup>	Case-referent	261 Incident CSCC	298 Population-based	Ever used OR = 1.6 (1.0–2.5) Last used $\geq 25$ yrs OR = 2.7 (0.9–8.5)	Frequency matched by age and sex. Results controlled for age, pigmentation, sunburns, sunbaths, and education.
Asgari et al, 2010, Northern Calif. <sup>42</sup>	Case-referent (nested)	195 CSCC	679 HMO-based	Used in past year Univariate OR = 2.4 (1.2–4.8) Multivariable OR = 2.0 (0.91–4.5)	Individually matched on age at time of exam, sex, residential postal zipcode, year of health check-up. Used surrogate markers for sun exposure.
Vessey et al, 2000, England/Scotland <sup>126</sup>	Cohort	83 CSCC and BCSC	17,032 Hospital-based	Ever used RR = 0.9 (0.6–1.4)	Results controlled for age (5 year groups). No measure of sun exposure collected. Self reported cases.



2.7 (95% CI = 0.9–8.5);  $P_{\text{trend}} = 0.01$ ]. Among women who had used OCs for  $\geq 25$  years, those with no variant alleles for the XPD Lys751 Gln DNA repair gene (which is responsible for repairing UVR-induced DNA lesions) had a 4.4-fold greater OR (95% CI = 1.4–13.6) for CSCC than women with  $\geq 1$  variant alleles. A similar increased risk with OC use was observed in a nested case-control study using a large retrospective cohort of Kaiser Permanente Northern California members.<sup>42</sup> In this study, pre-diagnostic OC use was associated with a 2.4-fold OR (95% CI = 1.2–4.8) for CSCC in univariate analyses and with borderline statistical significance in multivariable analysis (OR = 2.0, 95% CI = 0.91–4.5). The multivariable risk likely was artifactually decreased in part due to over adjustment by variables associated with OC use but not with the outcome of CSCC. Information was not collected to assess a dose-response effect. A pooled effect analysis of the two studies yielded OR<sub>pooled</sub> = 1.7 (95% CI = 1.1–2.5).<sup>179,180</sup> Neither study adjusted for sexual behavior or presence of HPV.

### 3.2 Strength of the evidence

The propensity of OC use to increase risk for specific cancers in humans, including CSCC, remains uncertain due to various methodologic concerns.<sup>121,125,131,132</sup> For example, the frequent use of analgesics among women (aspirin, nonaspirin NSAIDs, and acetaminophen) is known to be inversely associated with concentrations of estrogen (estradiol,  $P_{\text{trend}} = 0.001$ ; free estradiol,  $P_{\text{trend}} = 0.01$ ; estrone sulfate,  $P_{\text{trend}} = 0.03$ ; ratio of estradiol to testosterone,  $P_{\text{trend}} = 0.04$ ) and could have confounded the results of studies that did not account for this variable when examining the association between OC use and cancer.<sup>133</sup> Certain antibiotics, anticonvulsants (except sodium valproate), and vitamin C similarly are known to interact with OCs.<sup>134</sup> Furthermore, changes over time in the formulation of OCs (eg, typical estrogen doses in the 1960s were more than twice the typical doses in the 1980s and since) must be considered when evaluating OC use and cancer risk.<sup>135,136</sup> Additional research is needed to determine whether OC use increases risk for CSCC among individuals with a specific hormone receptor profile, analogous to the increased risk for triple-negative breast cancer patients.

Although estrogen and progesterone receptors are present in normal skin,<sup>137,138</sup> CSCCs are not thought

to express significant amounts of sex hormones<sup>139</sup> and thus OCs probably do not significantly influence CSCC risk through sex hormone pathways.<sup>140</sup> However, OCs may operate through a non-sex hormone pathway such as p53.<sup>140</sup> Inactivation of the p53 gene is believed to play a pivotal gatekeeper role in SCC carcinogenesis, and estrogen appears to inhibit the actions of this tumor suppressor.<sup>141</sup> Estrogen also is believed to exert an antiapoptotic effect on cell growth through the activation of signaling pathways such as Src/Shc/ERK.<sup>138</sup> In contrast, risk for CSCC is increased in ovariectomized *Ptch1*<sup>+/-</sup> and Car-S mice,<sup>142</sup> while the incidence of CSCC is lower in women than men.<sup>41,81</sup>

The lack of a direct carcinogenic effect of OC use on CSCC does not rule out an interactive effect with another carcinogen such as HPV. Longterm OC use has been shown to enhance HPV transcription in cervical intraepithelial neoplasia and it could have a similar effect on development in CSCC.<sup>121,143</sup> OC use also could be non-causally associated with CSCC through increased sexual activity and exposure to HPV.

## 4. Human Papillomavirus Virus

### 4.1 Description and overview

HPV is a short sequence (eg, 7200 to 8000 base pairs of closed-circular double-stranded DNA of approximately 8 kbp), epitheliotropic, nonenveloped DNA virus that belongs to the papovaviridae family of viruses.<sup>144</sup> Over the 30 years since the first types were isolated,<sup>145</sup> approximately 118 papillomavirus (PV) types have been identified, and nearly 100 are known to infect humans.<sup>146</sup> Current data support the existence of more than 200 HPV types based on the detection of subgenomic amplicons.<sup>146–148</sup> The papilloma family of viruses is classified into 8 genera identified by Greek letters (alpha, beta, gamma, delta, kappa, mu, nu, xi), of which only two do not contain HPV types (delta, kappa).<sup>147</sup> Genera and species containing cutaneous HPV types include alpha (species 4, 8), beta (species 1), gamma (species 1), mu (species 1, 2), and nu (species 1).<sup>147</sup> Beta-PV types [previously referred to as epidermodysplasia verruciform (EV) types] thus far fully sequenced include 5, 8, 9, 12, 14, 15, 17, 19–25, 36–38, 47, 49, 75, 76, 80, 92, 93, and 96.<sup>149</sup> All HPVs contain at least seven early genes (E1–E7), two late genes (L1–L2), and an upstream regulatory region that control most transcriptional events of the HPV genome.<sup>150</sup> Evidence of an oncogenic role for

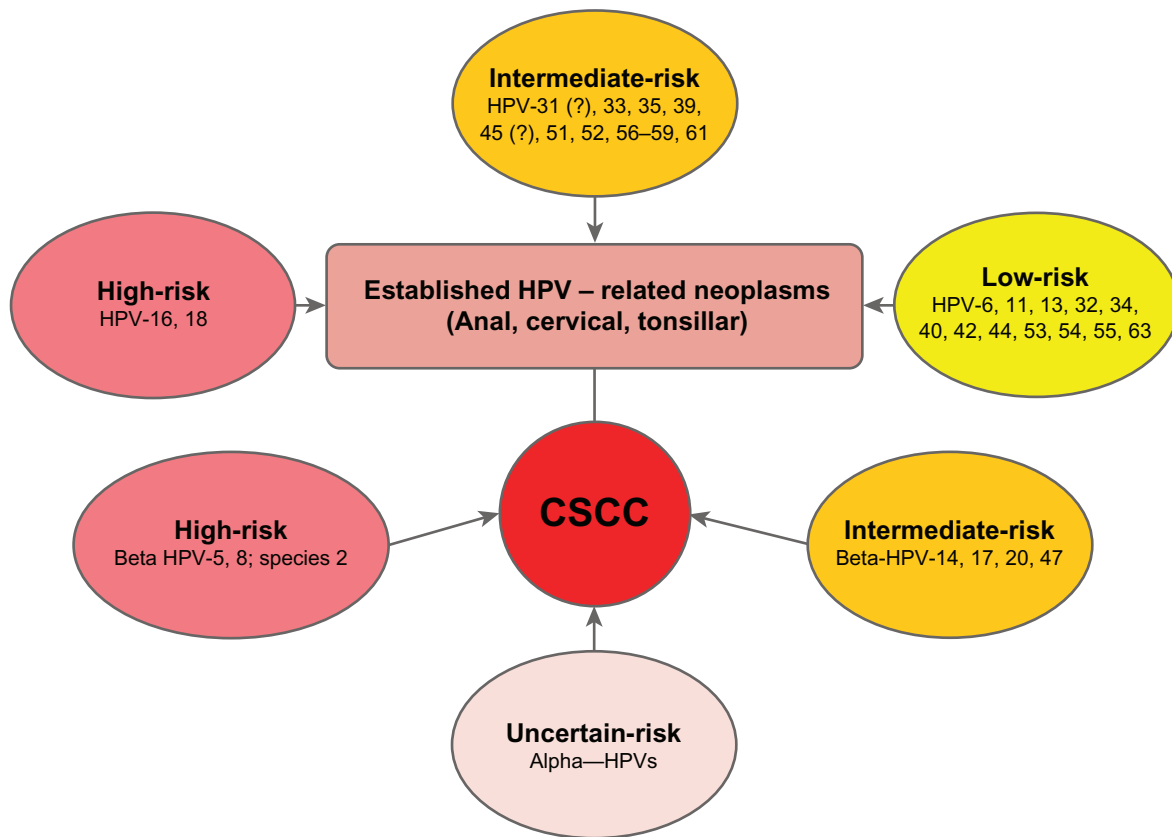


papilloma virus in CSCCs was first found in a study of Shope papilloma virus, which causes skin papillomas in rabbits.<sup>151,152</sup> Treatment of skin with a chemical co-carcinogen frequently induced transformation of rabbit papillomas into CSCC. However, animal PVs are not known to infect humans, as is the case for some other viruses like influenza, HIV-1, Ebola, or SARS.<sup>147</sup>

CSCCs mainly have been associated with beta- and gamma-PVs,<sup>75</sup> although alpha-PVs usually linked with anogenital SCCs are found in SCCs of the hand, finger, nail, and toe.<sup>5,153-173</sup> Except in immunosuppressed patients or individuals with the hereditary disorder EV, beta- and gamma-papillomaviruses normally are associated only with asymptomatic infections.<sup>147</sup> Although beta- and gamma-PVs are widespread, they contain many HPV types that remain to be sequenced and formally described.<sup>147</sup> Some novel cutaneous types such as HPV-109 have an uncertain classification because of an equal similarity in the L1 gene to different genera.<sup>174</sup>

Virtually 100% of the population is exposed to one or more HPV types in their lifetime,<sup>175,176</sup> and most individuals will not develop skin or other cancers potentially associated with the virus. Although a broad spectrum of HPV types frequently are detected in normal skin<sup>175,177-179</sup> and actinic keratoses (AK),<sup>180</sup> this fact does not preclude a pathogenic role in skin cancer since the presence of the virus should precede tumor development.<sup>17</sup> Similarly, a large portion of the population has been exposed to the ubiquitous Epstein-Barr virus and do not develop nasopharyngeal carcinoma, even though the virus is a well established risk factor for the cancer.<sup>175</sup> HPV is more frequently found on the forehead than on less sun exposed areas such as the thighs, possibly indicating a role for local photoimmunosuppression in the colonization of cutaneous HPV.<sup>180</sup>

The oncogenic potential of specific HPV types has been based primarily on data from anogenital and oral cavity SCCs and their precursor lesions (Fig. 2). HPV types 16 and 18 have a high risk for malignant progression, while HPV types 31, 33, 35, 39, 45, 51, 52, 56-59,



**Figure 2.** HPV types and cancer risk.  
**Note:** In contrast to anal, cervical and tonsillar cancers, the role for alpha HPVs remain uncertain for most CSCCs.



and 61 have been traditionally categorized as having intermediate risk of progression.<sup>181,182</sup> The inclusion of HPV 31 and HPV 45 into the intermediate group likely will be readdressed in the future. Benign lesions typically harbor HPV types 6, 11, 13, 32, 34, 40, 42, 44, 53, 54, 55, and 63,<sup>181,182</sup> although some benign types have been implicated in SCCs outside of the anogenital region (eg, oral cavity cancer<sup>183</sup> and paranasal sinus dysplasia<sup>184</sup>). Supposedly benign non-genital warts containing HPV-1 also have been reported to manifest Bowenoid histologic features<sup>185</sup> and they appear capable of converting to CSCC under the influence of UVR and immunosuppression.<sup>186</sup> HPV-2, which is classically associated with palmoplantar warts, has been found in verrucous carcinoma of the foot.<sup>187</sup> Many of the virus types detected in the anogenital tract are seen in both squamous intraepithelial lesions (carcinoma in situ) and invasive squamous cell cancers of the skin, albeit with different frequencies and risk distributions. Other HPV types are unique to the skin.<sup>78,188–190</sup> High risk mucosal types found in CSCCs include HPV-16, -18, -51, -54, -56, -61, and -69.<sup>189,191,192</sup> Among OTRs, low risk HPV types 6 and 11 are frequently found in benign, premalignant, and malignant cutaneous lesions.<sup>192</sup> Mixed type HPV infections within a single lesion are commonly observed in immunosuppressed patients, but less frequently in CSCCs in the general population.<sup>78</sup>

Oncogenic HPV types are believed to promote tumor progression by expressing E6/E7 viral oncoproteins. These proteins act on cyclins E and A to stimulate cell proliferation,<sup>181</sup> disrupt the p53-mediated cellular response to DNA damage, and induce the degradation of the retinoblastoma tumor suppressor gene product (pRB) through the proteasome.<sup>193–195</sup> HPV-16 DNA is capable of integrating into the genome of epithelial tumor cells and altering transcription, as shown by the expression of E6 and E7 in derived cell lines.<sup>196</sup> Immortalized human keratinocytes created in the laboratory by injecting DNA from HPV into the cells have been shown to become tumorigenic after chronic exposure to benzo(a)pyrene.<sup>197</sup> High levels of E6/E7 protein expressed by HPV-16 stimulate apoptosis through the release of IL-1 $\alpha$  from keratinocyte cell cultures.<sup>198</sup>

Studies of E6 in cutaneous beta HPVs indicate that this protein gene product has the potential for oncogenic transformation, though to a considerably lesser degree than high risk alpha-HPV types, and

transformation probably depends on interaction with other co-carcinogens to cause mutations in the host cell genome.<sup>181</sup> For example, the expression of the HPV-8 E6 open reading frame (ORF) is able to induce morphologic transformation in rodent fibroblasts but lacks the capability to transform NIH 3T3 cells or human keratinocytes in vitro as shown for high-risk HPV-16 and HPV-18.<sup>76,199,200</sup> Morphologic transformation in a rat fibroblast cell line, 3Y1, also has been observed for the E6 gene of HPVs 5, 8, 47, and less potently for HPVs 14, 20, 21, and 25.<sup>201</sup> The E6 protein consists of five regions delimited by two zinc-finger domains, the second of which is believed to be the key transforming element.<sup>201,202</sup> Several cutaneous HPV types produce E6 proteins, which have been shown to induce apoptosis in response to UVR damage in tissue culture experiments.<sup>203–205</sup> At the same time, a p53-independent pathway for HPV viral oncoproteins capable of inducing mutations<sup>206</sup> and interrupting apoptosis in response to DNA damage<sup>207,208</sup> may play a role in a subset of HPV-related cancers.<sup>209</sup> Interestingly, E6 proteins of HPV-1, HPV-8, and HPV-16, but not HPV-6, have been shown to bind to XRCC1 (a polypeptide implicated in the repair of various DNA single-strand breaks) and impair single-strand break repair.<sup>210</sup>

HPVs reside ubiquitously, often in a latent state, in the skin and mucosal epithelia.<sup>146,181,211,212</sup> A specific trophic affinity is seen for squamous epithelial cells at specific sites in which the complete replicative life-cycle of HPV is limited to this cell type.<sup>150,213,214</sup> HPV infection and related neoplasms occur at greater than expected rates in individuals who are immunosuppressed,<sup>215–223</sup> suggesting that impaired cell-mediated immunity, whether of iatrogenic origin, or related to HIV infection and/or other causes, plays an important role in the early transition from latency to the overt presentation of HPV-related disease.<sup>218</sup> Evidence suggests that late-stage cancer invasion is not greatly influenced by immune status,<sup>224</sup> and other factors such as genetic change may be more directly involved in the later progression from high-grade HPV-related disease to cancer.<sup>181,216–218,225,226</sup>

## 4.2 Route of transmission

Most studies suggest a positive association between sexual behavior (eg, young age at first intercourse,



high lifetime number of sexual partners, sex with non-monogamous partners, and other sexually transmitted infections) and HPV infection in anogenital disease.<sup>211,227–237</sup> A higher than expected concordance of HPV infection in sexual partners also suggests venereal transmission.<sup>238–242</sup> HPV is spread in a non-hematogenous fashion (eg, infection primarily occurs at sites where the virus enters the body such as the genital tract, skin, and oral cavity) without a viremic phase, and probably is clinically significant as a consequence of ongoing sexual behaviors and persistent re-infection.<sup>219,243–246</sup>

Horizontal skin-to-skin contact in humans has been documented in several reports, however questions remain regarding whether the infection is largely transient and non-productive.<sup>143</sup> The presence of HPV alone does not necessarily imply infection.<sup>143</sup> In one study, the detection of same types of HPV on the female hand and the male genitals of heterosexual couples suggested hand carriage as a pathway for HPV infection.<sup>247</sup> Couples experiencing HPV transmission in this study were more sexually active and were more likely to use nonbarrier forms of contraception. Male self-inoculation also was observed to occur and was attributed to casual contact or masturbation. The feasibility of HPV transmission through sex related skin-to-skin contact also was demonstrated in a cross-sectional study which found that co-habiting partners of the opposite-sex shared a greater number of beta-PV types than either shared with randomly selected matched members of the population.<sup>248</sup> Among participants in this study with at least one virus infection (26 couples), 74% of the partners and 46% of the control pairs shared at least one type ( $P = 0.02$ ). In another study, transmission of beta-PV between individuals who were living in close proximity (but were not sexually intimate) was rare; suggesting that casual contact alone probably is insufficient for infection in most cases.<sup>179</sup> Surprisingly, genital examinations of patients with digital CSCC and of their spouses have not revealed simultaneous genital SCC lesions.<sup>249</sup> However, a history of a genital SCC successfully treated many years prior to the diagnosis of a digital SCC (both lesions revealed the same oncogenic HPV subtype) suggests that a very long delay may intervene between a genital SCC and a subsequent HPV-related digital CSCC.<sup>169,173,249</sup>

The isolation of HPV DNA in fomites on equipment after examination of patients with genital HPV infections provides further evidence that high-risk genital HPV can survive outside the mucosal environment and may even be transmitted through sex toys and massage instruments.<sup>250</sup> Samples collected from the bedroom floor of infected individuals also have tested positive for HPV DNA.<sup>277</sup> Further research is needed to determine whether horizontal transmission of HPV between sexual partners through intimate skin-to-skin contact (with or without penis penetration) is possible and represents a clinically meaningful source of infection.

### 4.3 HPV persistence and clearance

Very little is currently known about either the persistence or clearance of HPV infection in the skin. However, in the anogenital area, where the persistence of HPV infection is believed to be an important prerequisite for the development of most cervical intraepithelial neoplasias and cancers,<sup>242,243,251–253</sup> HPV type 16 [relative risk (RR) = 0.47, 95% CI = 0.32–0.72], and to a lesser degree types 31, 33, 35, 52, 58) (RR = 0.62, 95% CI = 0.47–0.94), were observed to have a lower clearance rate than low risk types.<sup>245</sup> This finding also has been noted in several previous studies.<sup>244,246,254–259</sup> In one study, infection with single and multiple HPV types had similar clearance rates, eg, type-specific HPV clearance was independent of co-infection with other types.<sup>245</sup> However, in another study, HPV persistence was associated with multiple HPV types.<sup>257</sup> A dose-response relationship between viral load and persistence of HPV infection has been found in some<sup>244,260</sup> but not all studies.<sup>245</sup>

Genital HPV-16 infection typically clears within 2 years if an intact immune response is present (eg, fully functioning T helper/inducer, Langerhans, and natural killer cells).<sup>233,244,245,257,261,262</sup> In fact, less than half of HPV infections persist 6 months.<sup>245</sup> Some studies indicate that HPV infection has a greater tendency to persist in older women which may be explained by hormonal changes and/or lifestyle differences among older women,<sup>245,261</sup> or reactivation of latent disease in some women as they age and their immune surveillance diminishes.<sup>263</sup> However, other studies have not observed an older age effect for HPV infection.<sup>264–266</sup> Among women 20–29 years old, younger age was a risk factor for oncogenic HPV infection.<sup>267</sup> In a large population-based cohort analysis, determinants of





HPV-16 seropersistence included having one sexual partner during the follow-up period and former oral contraceptive use.<sup>264</sup> A 14-fold estimated risk for cervical cancer was observed for women who had at least three positive tests for high-risk HPV than for those who had negative results.<sup>258</sup>

In contrast to genital HPV, the acquisition of cutaneous HPV appears to first occur in early infancy, posing an inherent obstacle to effective vaccine development.<sup>268,269</sup> This also suggests other means of spread than sexual. Specific HPV types may persist in normal skin<sup>269,270</sup> or benign skin lesions<sup>271</sup> over long periods of time. Approximately half (48%) of healthy individuals have been found positive for the same cutaneous HPV type after 6 years of follow-up.<sup>272</sup> Also, beta-PV type specific persistence in plucked eyebrow hairs was observed over a period of at least 6 months in 74% of the participants examined in a 2-year follow-up study of healthy adults.<sup>179</sup> Similarly, 30% of the total beta-PV detected 7 years earlier in hair samples was found to persist at later follow-up.<sup>149</sup> DNA from multiple beta-PV also has been detected in follow-up at 6 months or longer.<sup>179</sup>

The presence of an endogenous reservoir for HPV is believed to be an important factor underlying the persistence of this virus. In the anogenital and oral cavities, the mucosal environment appears to serve as a receptive reservoir for HPV infection. The lack of a similar mucosal reservoir for the skin suggests that HPV may not play a role in the etiology of CSCC comparable to that in anogenital or oral cancer. However, hair follicles may act as a possible reservoir for cutaneous HPV, based on the high number of samples testing positive for the virus<sup>17,273–275</sup> and the concurrence of same type HPV-positive pairs in skin cancer biopsies and plucked eyebrow hairs.<sup>276</sup> Also, in hair samples obtained from the head region, HPV typing has revealed the presence of multiple HPV types, including those associated with genital infection.<sup>17</sup>

#### 4.4 Epidemiologic evidence of HPV in CSCC

In contrast to the role of high-risk HPV types in anogenital cancers, the epidemiologic data to date do not support a necessary role for these HPV types in CSCC, given the large number of negative cases. The ubiquitous presence of cutaneous HPV in non-cancerous

skin<sup>176,177,270,272,277,278</sup> and the long-lasting HPV warts observed in transplant recipients<sup>11</sup> further indicate that skin-borne HPV infection is not an absolute cause of CSCC. Rather, risk appears to involve an interaction between other carcinogens (eg, sunlight, immunosuppression, chemicals, hormones, and radon), race, and genetic factors. For example, a statistically significant relationship has been observed between increased time spent outdoors and detection of HPV in healthy skin.<sup>278</sup> Similarly, HPV DNA was significantly associated with sites extensively exposed to the sun, in both lesions and healthy skin samples.<sup>279</sup> However, one study found no convincing evidence of an association between beta- or gamma-PV seroprevalence and measures of sun sensitivity or UV exposure.<sup>280</sup> Evidence of a supportive rather than a direct role for cutaneous HPV types in CSCC also is shown by the difficulty of obtaining positive cell lines for these HPV types, the inability of these viruses to immortalize human cells and degrade p53, and the relatively low number of viral genomes detected per cancer cell.<sup>17,181,281,282</sup> Although integrated beta-PV has been isolated from a metastatic CSCC in an OTR, most of the evidence suggests that beta-PV is episomal in both AK and CSCC.<sup>175,283</sup> However, integration of HPV DNA into host chromosomal DNA is not absolutely required for malignant transformation to occur as has been observed by Sánchez-Lanier and colleagues.<sup>155</sup> It remains to be determined whether HPV has a non passenger role in the etiology of CSCC.<sup>284</sup> In contrast, HPV related cancers of the anogenital track meet the epidemiologic, molecular, and functional criteria of the World Health Organization (WHO) for viral carcinogenesis.<sup>284</sup> Three types of epidemiologic research described below provide support for the role of HPV in the etiology of CSCC.

##### 4.4.1 Epidermodysplasia verruciforms (EV)

A link between beta-PVs and CSCC was first observed in patients with the rare inherited disorder EV, which is characterized by a defect in cell-mediated immunity.<sup>285</sup> In this condition, individuals develop persistent viral warts at a young age (eg, 4–8 years) on UVR-exposed areas of the body that progress in about 30% of cases to CSCC during middle age.<sup>178,286</sup> EV related CSCCs test positive for HPV-5 and –8 in 90% of cases<sup>287</sup> and for HPV-14, –17, –20, and –47 less frequently.<sup>76,287</sup> The HPV types found in EV-related skin cancers also are



detected in approximately 80% of CSCCs of OTRs,<sup>288</sup> but CSCCs of OTRs typically have lower viral loads than the CSCCs of non-OTRs.<sup>190,284,289</sup> Oddly, antibodies against EV-HPV are not common in the northern European population.<sup>75</sup> EV-HPV DNA has been shown to be transcriptionally active in some CSCCs, indicating that EV-HPV may contribute directly to the pathogenesis of CSCC.<sup>70</sup> However, to date it has not been possible to demonstrate *in vitro* transformation of human keratinocytes using EV-HPV or the formation of tumors in nude mice by EV-HPV-8 E6 transformed fibroblasts.<sup>78,200</sup> Occasionally, p53-positive EV tumors have been observed in nonexposed skin, suggesting that factors other than UVR exposure may play a role in this cancer.<sup>285</sup>

#### 4.4.2 Organ transplant recipients

A double-digit or greater increased relative risk for CSCCs among iatrogenic immunosuppressed OTRs has been observed in several studies.<sup>12,284,290–294</sup> And risk appears to be greater for specific immunosuppressive regimens.<sup>295,296</sup> The tumors occur on average 6 to 7 years following transplantation and typically appear on sun-exposed sites.<sup>76</sup> Up to 70% of OTRs experience a NMSC by 20 years after transplantation, and the majority are CSCCs.<sup>290,297</sup> Most CSCCs are characterized by multiple types of HPV infection.<sup>78</sup> While EV-HPV is the predominant type found in this malignancy, cutaneous HPV types are found in approximately 50% of lesions, and less frequently, mucosal HPV types (<15%).<sup>78</sup> While premalignant skin lesions and viral warts are highly prevalent in HPV infection and might indirectly suggest progression from less dysplastic forms to invasive CSCC,<sup>78,190,298,299</sup> it should be noted that the distribution of HPV types in viral warts generally differs from that observed in precancers or CSCCs.<sup>297</sup> Although OTRs receive better than average clinical follow-up, surveillance bias alone probably does not explain the 250 times higher incidence of CSCC among OTRs than in the general population.<sup>291</sup>

#### 4.4.3 Association studies

In contrast to the widely accepted epidemiologic evidence linking high-risk HPVs to cervical cancer, the role of HPV in CSCC remains unclear. A retrospective study of immunocompetent participants, controlling

for age, sex, and sun exposure to the head, face, neck, forearm, hands, and lower limbs observed a 32-fold greater OR (95% CI = 10–100) for CSCC among those testing positive for DNA HPV than for those testing negative.<sup>297</sup> A 59-fold adjusted OR (95% CI = 5.4–645) for NMSC was reported for the subset of cases testing positive for high-risk HPV mucosal types (16, 31, 33, 35, and 51). An adjusted OR was not reported, but the crude OR for CSCC among those testing positive for high-risk HPV mucosal types was 31 (95% CI = 3.8–258). The prevalence of HPV infection in normal skin was low (4.7%), however, compared with a previous report,<sup>178</sup> suggesting that ORs in this study may have been inflated. Furthermore, the percentage of mucosal types detected on the hands/fingers versus other sites was not specified in the study. HPV-16 is rarely found in non-genital, nondigital, CSCCs in healthy immunocompetent individuals.<sup>249,300</sup> In another case-control study of immunocompetent individuals, DNA from beta-PV species 2 was found more frequently in CSCC than in adjacent healthy skin (OR = 4.0, 95% CI = 1.3–12), indicating a possible differential risk by specific beta-HPV types.<sup>301</sup> The results of this study are difficult to interpret, however, since 1) *in situ* hybridization to determine viral load was not performed, and 2) tissue samples apparently were not “stripped” to reduce surface contamination.<sup>302</sup> The significant differences also may have been attributable to chance since results were not adjusted for numerous (>45) multiple comparisons. Nonetheless, the findings were similar to those of a previous study which observed a 4.40 OR (95% CI = 1.92–10.06) for CSCC in association with beta-PV species 2.<sup>279</sup> Neither of the above two studies addressed the possibility that the differentially greater prevalence of beta-PV infection was the result of changes to the immune system caused by the cancer.

Several association studies which tested for beta-PV antibody positivity have found an increased risk for CSCC,<sup>60,303–305</sup> and risk was greater in the presence of a susceptible phenotype (gender, skin color, propensity to burn) or high lifetime sun exposure.<sup>304,305</sup> No difference in HPV seropositivity has been found between BCSC patients and controls.<sup>304</sup> The increased risk for CSCC does not necessarily imply causality since it is not possible to determine the origin of HPV infection (eg, skin, oral cavity, anogenital area) or the



exact timing of infection when using antibody testing. Given the ubiquity of the virus and the relatively low number of seropositives, the majority of antibodies directed at HPV probably are generated near the time of tumor formation, suggesting reverse causality.<sup>303</sup> Furthermore, not all infected women test positive for antibodies against HPV, due in part to the extended period necessary for the immune system to produce these proteins, or to the lack of a sustained antigenic exposure and/or a low viral load.<sup>306–308</sup> Positive associations for CSCC have been reported when using a degenerate and nested polymerase chain reaction (PCR) technique to assess HPV positivity in normal skin<sup>309</sup> or plucked eyebrow hairs.<sup>310</sup> However, the concordance between specific HPV types in normal and proliferative lesions from the same individual was low.<sup>309</sup> Overall, PCR results must be interpreted cautiously since HPV detection by this method is not necessarily equivalent to infection with HPV<sup>188</sup> and alternatively could be a contamination or a passerby. PCR also does not provide information about the intracellular localization of viral DNA.<sup>17</sup>

Allograft recipients are especially susceptible to NMSCs and anogenital dysplasia/cancer,<sup>299</sup> raising the question of whether HPV is a possible common risk factor in both diseases. For example, renal allograft recipients (RARs) classified with  $\geq 4$  intra-epidermal carcinomas (IECs) or invasive CSCCs have been found significantly more likely to develop potentially life-threatening multiple anogenital tract neoplasms than less susceptible RARs ( $< 4$  IECs or CSCCs).<sup>211</sup> Similarly, in the general population an increased risk for CSCC has been observed after anogenital cancer, and conversely, an increased risk of anogenital cancers has been observed following CSCC, although risk estimates varied widely by histologic category and gender.<sup>112–114,312,313</sup> For example, a 20-fold standardized incidence ratio (SIR) for CSCC has been observed following anal cancer among women during the first year of follow-up, but not among men.<sup>112</sup> The increased risk of non-Hodgkin's lymphoma observed following CSCC appears to indicate that immune suppression, rather than HPV, is the mechanism underlying both cancers, since HPV is not known to be a risk factor for non-Hodgkin's lymphoma.<sup>314</sup> Exposure to UVR has been suggested as a common risk factor because

of its effects on the immune system and the similar temporal trends and geographic patterns that exist for non-Hodgkin's lymphoma and CSCC.<sup>97</sup>

#### 4.5 Strength of the evidence

Proof that HPV infection is causally related to CSCC awaits definitive laboratory and epidemiologic confirmation.<sup>188,315</sup> A consistent understanding of cutaneous HPV infection and CSCC risk is lacking largely because of methodological difficulties in HPV detection and reproducibility.<sup>309</sup> The interpretation of results is further complicated by the so-called “hit and run” hypothesis, according to which HPV may be important only for the initiation, not the maintenance of the transformed cellular phenotype.<sup>175,288,316</sup> Indeed, the number of beta-PV genome copies per tumor cell in AK (the precursor lesion of CSCC) is approximately 10-fold higher than in CSCC.<sup>74,175,317</sup> This raises the question of an etiologic role for HPV even though the resulting CSCCs lack HPV viral genes or proteins.<sup>318</sup> Nonetheless, no cutaneous “high-risk” HPV types on par with genital HPVs have been identified.<sup>279</sup> Nor has any beta-PV type been shown to cause CSCC in experimental systems,<sup>149</sup> although in one study 6% (9 cases) of backcrossed mice, transgenic for the HPV-8 early region under control of the keratin 14 promoter, spontaneously developed invasive SCC appearing lesions without any treatment with physical or chemical carcinogens.<sup>319,320</sup> Furthermore, the detection of beta-PV in CSCC, in the absence of other evidence, does not prove causation. For example, beta-PV may occur as a consequence of immunosuppression, similar to other non-oncogenic opportunistic infections (eg, cytomegalovirus, herpes simplex virus, molluscum contagiosum, aspergillosis, and candidiasis).

The mechanism by which HPV causes CSCC, if that is the case, would appear to differ from that of other known HPV-related neoplasms. In the case of the cervix, anus, and tonsils, HPV tends to cause cancer in “transformation zones” where one kind of epithelium transitions within a defined boundary into another type of epithelium through a process known as metaplasia (eg, columnar epithelium into squamous epithelium).<sup>321</sup> A comparable transformation zone does not exist for exposed skin, with the exception of the eyelids, lips, and periungual region. Furthermore, oncogenic genital HPV types are able



to bind to and degrade p53 through the proteasome in contrast to cutaneous HPV types.<sup>203,322,323</sup>

## 5. Interactions between OCs and HPV

Much of the work on the possible effects of estrogen and OCs on HPV prevalence has focused on the inflammatory and immune regulatory properties of this hormone in the uterus.<sup>324</sup> Response variations in these properties are thought to be important determinants of the viral persistence and progression underlying the development of SCC.<sup>325,326</sup> Estrogen is known to cause an influx of neutrophils and macrophages, tissue edema, and proliferation of uterine epithelial cells.<sup>324</sup> Additionally, OCs alter the expression of certain regulatory cytokines, such as IL-10 and IL-12, in the cervical mucous.<sup>325</sup> Results reflect the down-regulation of immune markers in the cervix, corresponding to changes in reproductive hormones observed in animals during the menstrual cycle.<sup>327</sup> Overall though, reproductive hormones appear to enhance immunity.<sup>327,328</sup>

A consistent picture has yet to emerge regarding the influence of OCs on HPV infection and the subsequent development of SCCs. In a pooled case-control study of cervical cancer, neither OC use nor increasing dose was significantly associated with HPV positivity among controls, suggesting that OCs do not have a facilitating role in HPV infection or persistence.<sup>329</sup> Indeed, current use of OCs had a significantly protective effect on the follow-up incidence of HPV [hazard ratio (HR) = 0.49, 95% CI = 0.28–0.86].<sup>330</sup> Similarly, in a study of atypical squamous cells of undetermined significance (ASCUS), oncogenic HPV was less common in women who were using oral contraceptives, although the difference was not statistically significant ( $P = 0.15$ ).<sup>331</sup> In a crude analysis, approximately 35% of current OC users, compared with 26% of referents, were identified with prevalent cervicovaginal HPV (OR = 1.52, 95% CI = 1.03–2.32); however, the difference was not statistically significant after adjustment for various demographic, sexual, and lifestyle factors.<sup>232</sup> Similarly, positive univariable but null multivariable results were observed in an analysis of the third National Health and Nutrition Examination Survey (NHANES III).<sup>332</sup> Three additional studies have not observed a statistically significant association between cervical HPV infection and OC use.<sup>230,231,237</sup>

In contrast, increased prevalence of HPV is seen in the lower genital tract of pregnant women.<sup>333</sup> After adjusting for age, number of lifetime and recent sexual partners, age at first intercourse, and smoking, former OC use (OR = 1.3, 95% CI = 1.1–1.5) and current OC use (OR = 1.5, 95% CI = 1.2–1.8) were associated with HPV-16 seropositivity in a large population-based cohort of 10,000 women in Costa Rica.<sup>334</sup> Regardless of duration, OC use [0 years, OR = 1.0; 1 year, OR = 2.2 (95% CI = 1.2–4.0); 2–3 years, OR = 2.1 (95% CI = 1.2–3.9); 4+ years, OR = 2.5 (95% CI = 1.2–5.1)] was associated with HPV infection (specific types not specified), independent of age, race, and lifetime number of male sexual partners.<sup>228</sup> When examined by HPV type, OC use was significantly associated with increased detection of HPV-16/18 ( $P = 0.04$ ).<sup>335</sup> Inexplicably, OC use appeared to decrease the risk of low grade squamous intraepithelial lesions whether women were positive or negative for HPV infection.<sup>335</sup> These discrepant findings, however, may be attributable to differences in study design, sampling strategies, and varying sensitivity, specificity, and accuracy of HPV detection methods.<sup>232</sup>

Supporting the role of estrogen in the malignant transformation of HPV infected cells into SCC, a laboratory study has demonstrated that estrogen stimulates the differential transcription of the E6/E7 and E1 genes of HPV-16 in SiHA cervical carcinoma cells.<sup>336</sup> Glucocorticoids, a class of compounds resembling the steroids found in OCs,<sup>335</sup> also have been shown to enhance the transformation of HPV-16 infected cell lines and increase the in vitro transcription and expression of the HPV-16 genome.<sup>337–339</sup>

Estrogen-induced squamous cell carcinogenesis has been demonstrated in the female reproductive tract of K14-HPV-16 transgenic mice,<sup>340</sup> and  $\beta$ -oestradiol has been shown to stimulate the in vivo growth of human condylomas induced with HPV in mice.<sup>336</sup> The possibility also exists that reproductive hormones may promote the integration of HPV DNA into the host genome,<sup>341</sup> which would be consistent with the observed increased risk for cervical cancer after prolonged use of OC.<sup>329</sup>

## Conclusion

The evidence to date does not support an independent or synergistic role for OC use in the development of



CSCC; nor does it fail to do so. Proof of association does not, of course, indicate a cause-and-effect relationship, as illustrated by the association between herpes genitalis and cervical carcinoma.<sup>316,342</sup> Many questions remain to be answered. OC use may simply be a surrogate marker for sexual activity<sup>343,344</sup> and non-causally associated with CSCC risk through increased exposure to HPV. This depends on whether HPV is a causative factor in CSCC, which remains controversial.<sup>315</sup> On the other hand, OCs may have a contributing biologic role in the cascade of events leading up to CSCC. For example, certain beta-PV types in combination with OC use may play an initiation role, while the promotion or progression of CSCC ultimately depends on UVR exposure.<sup>61</sup> The period between a hormonal exposure and the appearance of cancer may be lengthy, as illustrated by the development of vaginal cancer in daughters years after their mothers used diethylstilbestrol (DES) during pregnancy.<sup>345</sup> Notably, the above initiation/promotion model does not explain the occurrence of CSCC on predominantly non sun-exposed skin, suggesting that factors other than UVR also may be important promoters in the development of this cancer. CSCCs remain a major public health concern, ranking among the most prevalent and costliest cancers in the United States and serving as an important harbinger of secondary malignancies.<sup>346–348</sup>

The incidence of nonmelanoma skin cancer (in which CSCC is an important subtype) has approximately doubled since the mid 1990's.<sup>349</sup> Future large-scale studies that incorporate detailed epidemiologic information (eg, OC use, sexual history, molecular markers, and exposure to UVR, chemicals and HPV) and provide analyses stratified by in situ and invasive CSCCs and tumor location are needed to help unravel the complex picture of this disease.

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