Role of human papillomavirus in cutaneous squamous cell carcinoma: A meta-analysis

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Background: The role of human papillomavirus (HPV) in cutaneous squamous cell carcinoma (cuSCC) is not well defined, with past studies showing conflicting results.

Objective: We sought to determine if there is a significant association between HPV and cuSCC and whether cuSCC from immunosuppressed patients are more likely to carry HPV than cuSCC from immunocompetent patients.

Methods: We performed a systematic review and abstracted data from articles that included: skin samples by biopsy, HPV detection by polymerase chain reaction, and a minimum of 10 cases and 10 controls. Pooled effect size and 95% confidence intervals were calculated using random effects meta-analysis using the inverse variance method.

Results: cuSCC were more likely to carry HPV than normal-appearing skin (pooled effect size [ES] 3.43, 95% confidence interval 1.97-5.98, $P < .0001$) in all patients. An increase in HPV prevalence was found in tumors from immunosuppressed patients compared with immunocompetent patients (pooled ES 3.01, 95% confidence interval 2.00-4.52, $P < .0001$).

Limitations: The greatest limitation is the heterogeneity of the studies included. The association of higher HPV prevalence in squamous cell carcinoma compared with normal-appearing skin does not imply causality.

Conclusion: These results contribute to evidence that HPV is associated with cuSCC. Higher HPV burden in tumors from immunosuppressed patients compared with immunocompetent patients may have therapeutic implications. (J Am Acad Dermatol 2014;70:621-9.)

Key words: cutaneous squamous cell carcinoma; human papillomavirus; immunocompetence; immunosuppression; meta-analysis; skin cancer.

Nonmelanoma skin cancer is the most common cancer in the United States, and its incidence has continued to increase in the past 2 decades.[1] Among immunocompetent individuals, squamous cell carcinoma (SCC) is the second most common type of nonmelanoma skin cancer. Ultraviolet (UV) radiation exposure, fair skin, and immunosuppression are well-known risk factors for development of SCC.[2] The clinical behavior and epidemiology of SCC may also suggest a viral cause given the increased prevalence in organ transplant recipients compared with the general population

Abbreviations used:

CI:	confidence interval
cuSCC:	cutaneous squamous cell carcinoma
HPV:	human papillomavirus
SCC:	squamous cell carcinoma
UV:	ultraviolet

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and similar incidence to other virally induced cancers, including Kaposi sarcoma.[3]

One potential causative agent in SCC is human papillomavirus (HPV), as its role in cervical cancer is well established.[4,5] HPV also has an established causative role in verruca vulgaris, condyloma acuminata, various types of anogenital cancer, and some head and neck SCCs.[6,7]

However, HPV's relationship to cutaneous SCC (cuSCC) remains in question. Over 100 studies have investigated the relationship between HPV and cuSCC using different study populations, sampling techniques, detection methods, and HPV types. Only studies using biopsy specimens with polymerase chain reaction–based detection of HPV were included in the analysis.

The association of β-HPV types with SCC is clearly defined for patients with epidermodysplasia verruciformis, an autosomal recessive disorder characterized by an abnormal susceptibility to β-HPV (5 and 8 mostly).[8] However, the relationship between HPV and SCC in the general population is less well defined, as studies have yielded conflicting results. Although some studies have failed to find HPV in SCC, most studies report HPV infection in some SCCs (with variable percentages). Variable sampling and detection rates may have led to the wide disparity in prevalence.[9]

The objective of the current study is to perform a meta-analysis of the literature to determine the association between HPV and cuSCC. We also sought to determine whether there is a higher prevalence of HPV in SCCs from immunosuppressed patients compared with SCCs from immunocompetent patients.

CAPSULE SUMMARY

- The role of human papillomavirus in cutaneous squamous cell carcinoma has not been well defined.
- This meta-analysis contributes to the body of evidence that human papillomavirus is associated with cutaneous squamous cell carcinoma.
- These results may lead to more targeted treatment modalities for human papillomavirus-positive tumors, reduction of disease burden, and better patient outcomes.

METHODS

Search strategy and selection criteria

We systematically searched the biomedical electronic databases PubMed, Embase, Web of Science, CINAHL, and Cochrane Library for all relevant published literature as of June 22, 2012, using the key words "skin cancer" and "human papillomavirus" or "cutaneous squamous cell carcinoma" and "human papillomavirus." Duplicate articles were removed, resulting in a total of 3661 records. Titles and abstracts of articles were reviewed to screen for relevance and exclusion criteria. Reference lists from the retrieved studies and reviews were scanned to ensure that all potentially relevant literature was included, but no additional articles were found.

A total of 3290 articles were excluded for not being relevant; presenting no unique data; including patients with genodermatoses; including only lips, fingers, or genital samples; or unspecified nonmelanoma skin cancers rather than cuSCC. An additional 196 articles were not written in English. Our inclusion criteria are included in Table I. After screening using the aforementioned criteria, 17 articles qualified for the analysis examining tumor samples versus normal-appearing skin, and 12 articles were included for analysis of tumors from immunosuppressed individuals versus those from immunocompetent individuals (Fig 1). Three articles were used in both analyses as they met criteria for both.

Data collection and quality assessment

A standard data extraction procedure was created by B. A., J. W., and S. T. A. Each article was checked independently by J. W. and J. Y. for eligibility, and all relevant data were extracted independently and in duplicate for each article by B. A., J. W., and J. Y. Any discrepancies in the duplicates were settled by all authors in group discussion until a consensus was reached.

Data abstracted from each article included the year of publication, whether the assay was broad spectrum (detecting >10 HPV types) or limited spectrum (<10 HPV types), and types of HPV assayed (cutaneous, mucosal, or both). One article by Gustafsson et al[10] in 2004 reported cutaneous HPV type and mucosal HPV type assays separately but did not give aggregate numbers; these were considered as separate experiments. Numbers of SCC and normal-appearing skin from immunocompetent and immunosuppressed patients were extracted, as were numbers of HPV-positive and -negative specimens in each subgroup. "Squamous cell carcinoma" included tumors recorded as cuSCCs, keratoacanthomas, Bowen disease, and verrucous carcinomas. Bowenoid papulosis was excluded. "Normal-appearing skin" included both normal tissue from subjects with cuSCC and

Table I. Selection criteria for systematic review of articles

Exclusion criteria	Inclusion criteria
Not in English	1) Data based on biopsy samples (frozen tissue or formalin-fixed tissue) rather than eyebrow pluck, skin swab, or serology
Not relevant	2) HPV detection by PCR-based methods
Reviews	3) A minimum of 10 cases and 10 controls for determination of odds ratios
Letters to the editor	-For hypothesis 1: >10 normal-appearing skin controls and >10 SCC
Case studies with <10 samples (tumor or normal)	-For hypothesis 2: >10 SCC from immunosuppressed and >10 SCC from immunocompetent
Studies of patients with comorbid conditions (EV and other genodermatoses)	
Studies including only lips, fingers, and genital samples	
Unspecified NMSC	
Noncutaneous SCC	

EV, Epidermodysplasia verruciformis; *HPV*, human papillomavirus; *NMSC*, nonmelanoma skin cancer; *PCR*, polymerase chain reaction; *SCC*, squamous cell carcinoma.

normal-appearing skin from subjects without any cuSCC. Benign lesions were not included. When given, data were collected on the age, sex, immune status, and race of patients and whether the samples were from sun-exposed or sun-protected skin. Sun-exposed includes head/neck, arms, and hands. Sun-protected includes trunk and legs. Sites of interest exclude lips, fingers, and genital regions. In studies where biopsy sites were recorded, those collected from lips, fingers, and genital regions were excluded; as a result, the numbers in the tables may differ slightly from those published in a particular article. In studies that did not specify the exact location from which biopsy specimens were taken, all samples were included.

Statistical methods

Pooled effect size and 95% confidence intervals (CI) were calculated using random effects meta-analysis using the inverse variance (DerSimonian and Laird[11]) method. Heterogeneity between studies was assessed with 2 indicators, the I^2 and Q statistics. The I^2 statistic provides an estimate of the percentage of variability in the outcome that is a result of differences in exposure-outcome association; a significant Q statistic rejects the null hypothesis of homogeneity and indicates that the true effect size varies from study to study.[12]

Funnel plots were used to assess publication bias.[13] In a funnel plot the estimated effects are plotted against their SE. When publication bias is absent, the observed studies are expected to be distributed symmetrically around the pooled effect size. Begg rank correlation and Egger linear correlation tests were used to detect funnel plot asymmetry, with a threshold P value of .01. In the analysis of HPV prevalence in SCC versus normal-appearing skin, a trim-and-fill technique was used to adjust the random-effects model for possible publication bias.[14]

RESULTS

Hypothesis 1: tumors are more likely to carry HPV than normal-appearing skin

Seventeen articles met inclusion criteria (Table II).[10,15-29] SCCs were more likely to carry HPV than normal-appearing skin (pooled ES 3.43, 95% CI 1.97-5.98, $P < .0001$). The funnel plot showed no evidence of publication bias (Egger $P = .23$) (Fig 2).

There was significant evidence of statistical heterogeneity in the published studies, suggesting that individual study effect sizes varied based on differences study design ($I^2 = 76.0\%$, Q = 66.65 [degree of freedom (d.f.) = 16], $P < .0001$) (Fig 3). We investigated this with multiple methods including subgroup analyses based on the available covariates of broad- versus limited-spectrum polymerase chain reaction assays, cutaneous versus mucosal HPV types, and immunocompetent versus immunosuppressed subjects. These investigations yielded similar pooled effect sizes, ranging from odds of 2.61 to 4.99. Removing outliers at the 25th percentile resolved the heterogeneity to an I^2 statistic of 0%, $P = .85$, with minimal change in the pooled effect size (3.12, 95% CI 2.28-4.37, $P < .0001$).

Hypothesis 2: SCCs from immunosuppressed patients are more likely to carry HPV than SCC from immunocompetent patients

Twelve articles met inclusion criteria (Table III).[15,23,24,30-38] SCC from immunosuppressed patients are more likely to carry HPV than SCC from immunocompetent patients (pooled ES 3.01,

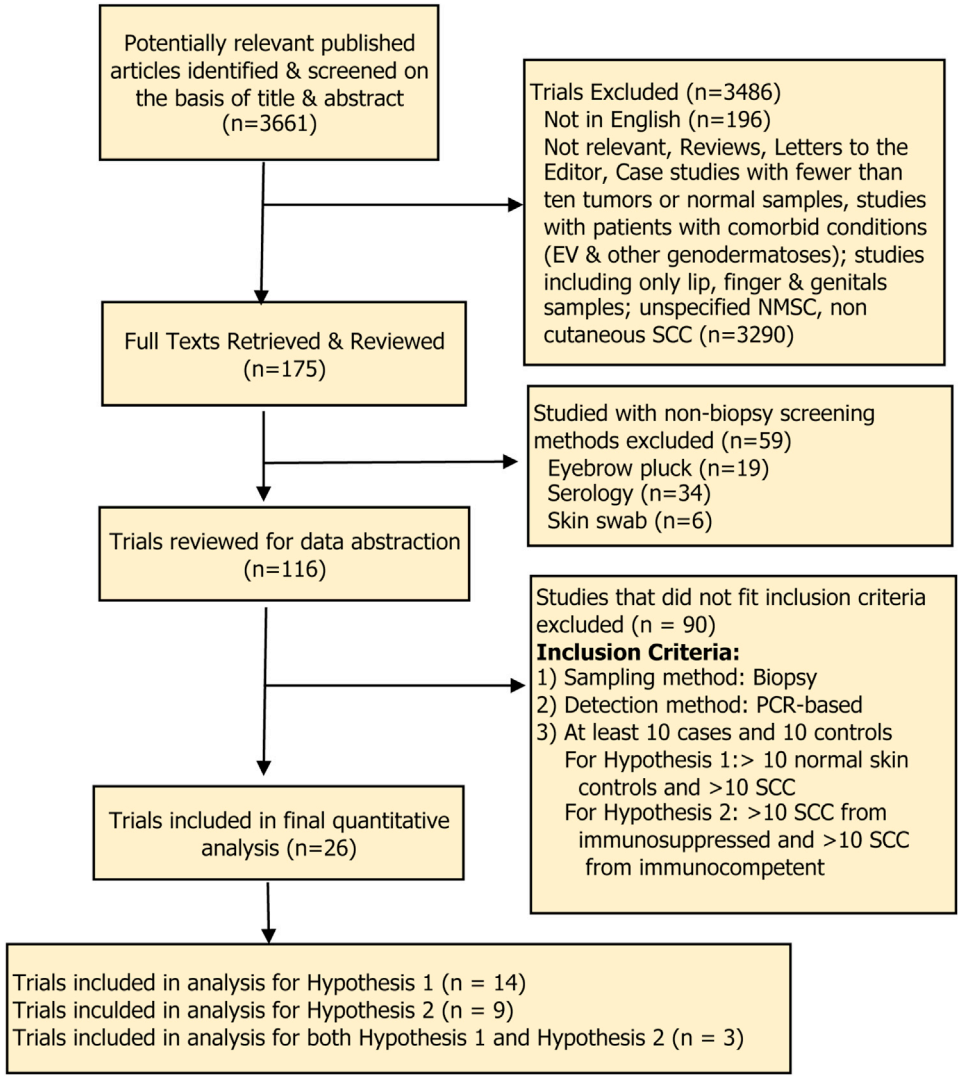

Fig 1. Flow chart of the search strategy and selection criteria. *EV*, Epidermodysplasia verruciformis; *NMSC*, nonmelanoma skin cancer; *PCR*, polymerase chain reaction; *SCC*, squamous cell carcinoma.

95% CI 2.00-4.52, $P < .0001$). There was minimal evidence of heterogeneity (I^2 = 28.4%, Q = 15.37 [d.f. = 11], $P = .17$) (Fig 4). The funnel plot showed no evidence of publication bias (Egger $P = .78$) (Fig 5).

DISCUSSION

The role of HPV as a causative agent for cuSCC remains a topic of controversy. Our objectives in this study were to perform a meta-analysis of studies attempting to define the association between HPV and cuSCC, and to determine whether cuSCCs from immunosuppressed patients are more likely to carry HPV than cuSCC from immunocompetent patients.

In the pooled data, cuSCC were more likely to carry HPV than normal-appearing skin (pooled ES 3.43, 95% CI 1.97-5.98, $P < .0001$). Tumors were more likely to carry HPV compared with normal-appearing skin in both immunosuppressed and immunocompetent patients; this relationship was slightly stronger for immunocompetent patients. Most of the studies analyzed used broad-spectrum polymerase chain reaction techniques (13/20). The types of HPV analyzed in the studies varied from mucosal, to cutaneous, to both mucosal and cutaneous. Sample sizes varied from 10 to 159 tumors with about half of the studies including over 50 samples. About three quarters of the studies were relatively recent (within the last 10 years) and none were older than 20 years. In general, the newer studies were broad spectrum and able to detect more HPV types.

Table II. List of articles included in the meta-analysis for tumor versus normal (hypothesis 1)

Source	HPV types	No. of HPV types	No. of HPV-positive patients (%)	
			SCC group	Control group
Strumia et al,[27] 1997	Mucosal	Limited	6 (60)	6 (37.5)
Hsi et al,[21] 1997	Mucosal	Broad	15 (21.7)	1 (3.8)
Berkhout et al,[17] 2000	Cutaneous	Broad	74 (74)	10 (32.2)
O'Connor et al,[25] 2001	Cutaneous	Broad	18 (85.7)	5 (17.2)
Meyer et al,[24] 2001	Both	Broad	39 (35.1)	10 (16.1)
Caldeira et al,[18] 2003	Cutaneous	Limited	12 (46.2)	4 (9.8)
Iftner et al,[22] 2003	Both	Broad	57 (62)	5 (4.7)
Gustafsson et al,[10] 2004 (EV type)	Cutaneous	Limited	1 (3.2)	5 (16.7)
Gustafsson et al,[10] 2004 (anogenital type)	Mucosal	Broad	19 (52.8)	8 (29.6)
Zheng et al,[29] 2005	Both	Broad	5 (13.2)	1 (2.1)
Hazard et al,[20] 2006	Cutaneous	Limited	3 (5.8)	2 (0.7)
Forslund et al,[19] 2007	Both	Broad	21 (25.6)	42 (12)
Asgari et al,[16] 2008	Both	Broad	46 (54)	103 (54.2)
Mackintosh et al,[23] 2009	Cutaneous	Broad	34 (56.7)	6 (33.3)
Zaravinos et al,[28] 2010	Both	Broad	4 (33.3)	8 (15.1)
Plasmeijer et al,[26] 2010	Cutaneous	Broad	17 (81)	17 (81)
Arron et al,[15] 2011	Cutaneous	Broad	20 (29.9)	5 (27.8)

EV, Epidermodysplasia verruciformis; *HPV*, human papillomavirus; *SCC*, squamous cell carcinoma.

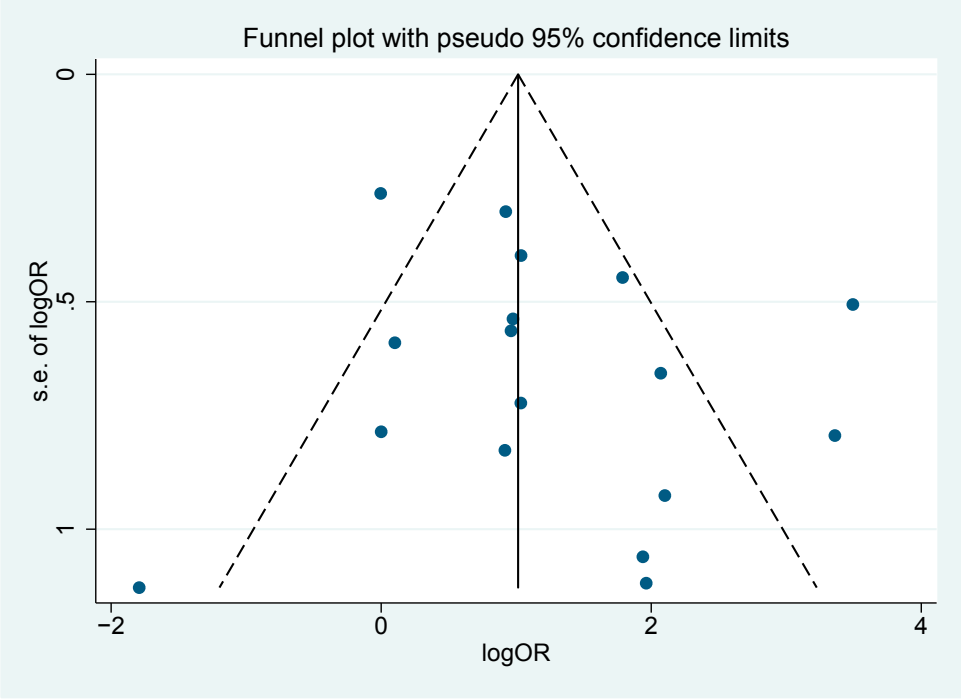

Fig 2. Funnel plot with pseudo 95% confidence intervals for tumor versus normal (hypothesis 1) showing no evidence of publication bias (Egger $P = .23$). *OR*, Odds ratio.

Compared with the immunocompetent population, an increased prevalence of HPV was found in tumors from immunosuppressed patients (pooled ES 3.01, 95% CI 2.00-4.52, $P < .0001$). This is not unexpected given that these patients harbor a greater burden of verruca vulgaris, which is known to be related to HPV infection.

The greatest limitation to analyzing the literature is the great degree of heterogeneity. As discussed previously,[9] variations in HPV type, sampling methods, and viral detection techniques all present challenges to grouped study analysis.

The association of higher HPV prevalence in SCC compared with normal-appearing skin does not

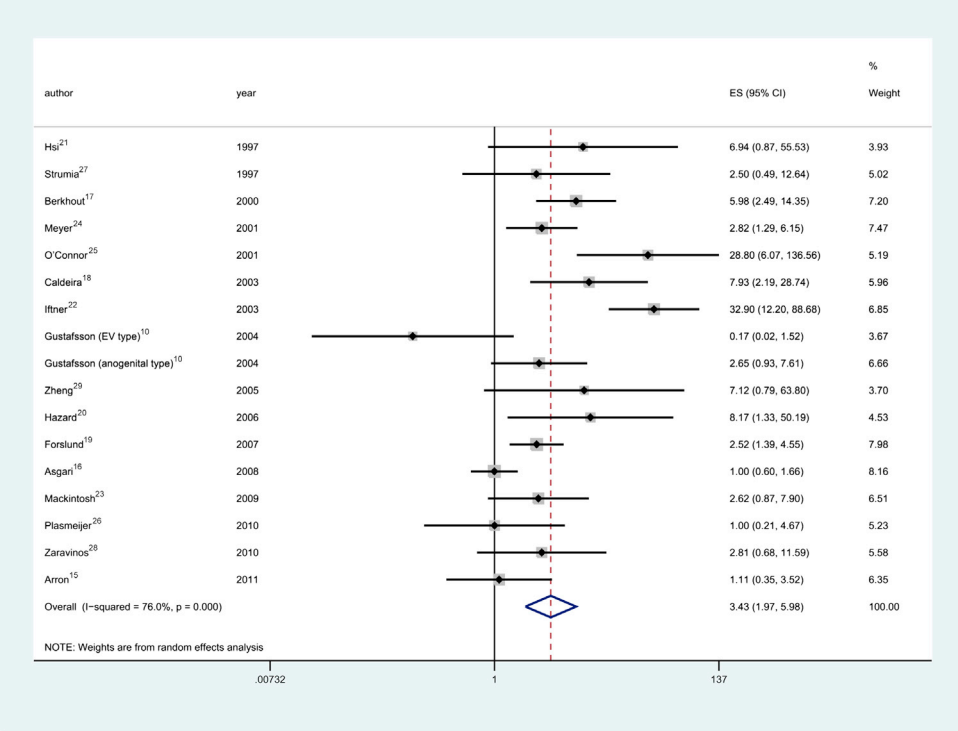

Fig 3. Pooled effect size and 95% confidence intervals (*CI*) for tumor versus normal (hypothesis 1), showing that squamous cell carcinomas were more likely to carry human papillomavirus than normal-appearing skin (pooled ES 3.43, 95% CI 1.97-5.98, $P < .0001$). I^2 and Q statistics showed significant evidence of heterogeneity in the published studies ($I^2 = 76.0\%$, Q = 66.65 [d.f. = 16], $P < .0001$). *EV*, Epidermodysplasia verruciformis.

Table III. List of articles included in the meta-analysis for immunosuppressed tumors versus immunocompetent tumors (hypothesis 2)

			No. of HPV-positive SCCs (%)	
Source	**HPV types**	**No. of HPV types**	**Immunosuppressed**	**Immunocompetent**
Shamanin et al,[38] 1996	Both	Broad	17 (70.8)	10 (33)
Arends et al,[30] 1997	Both	Broad	15 (51.7)	4 (26.7)
Harwood et al,[34] 2000	Both	Broad	37 (84.1)	6 (27.3)
Meyer et al,[35] 2000	Both	Broad	16 (76.2)	6 (54.5)
Meyer et al,[24] 2001	Both	Broad	12 (57.1)	27 (30)
Cairey-Remonnay et al,[31] 2002	Both	Broad	34 (64.2)	19 (37.3)
Forslund et al,[32] 2003	Cutaneous	Broad	33 (55)	4 (33)
Forslund et al,[33] 2003	Cutaneous	Broad	6 (54.5)	4 (33)
Purdie et al,[36] 2005	Cutaneous	Broad	63 (75)	6 (35.3)
Queille et al,[37] 2007	Both	Broad	15 (79)	14 (82.4)
Mackintosh et al,[23] 2009	Cutaneous	Broad	19 (56)	15 (57.7)
Arron et al,[15] 2011	Cutaneous	Broad	15 (38.5)	5 (17.9)

HPV, Human papillomavirus; *SCC*, squamous cell carcinoma.

imply causality. Lack of HPV presence in all SCCs may imply involvement in the initiation of oncogenesis, rather than tumor promotion or maintenance. Studies have demonstrated that HPV may not be necessary for the maintenance of SCC.[15] Also, not all SCCs may harbor the same genetic or cellular mutations. SCC may arise from actinic keratoses in the classic multistep model of oncogenesis. TP53 mutations caused by UV light–induced DNA damage, activating mutations in Harvey rat sarcoma (HRAS), and loss-of-function mutations in notch receptors that regulate normal squamous cell differentiation can all be seen in different tumors.[39] HPV may play a role in one pathway, but not others,

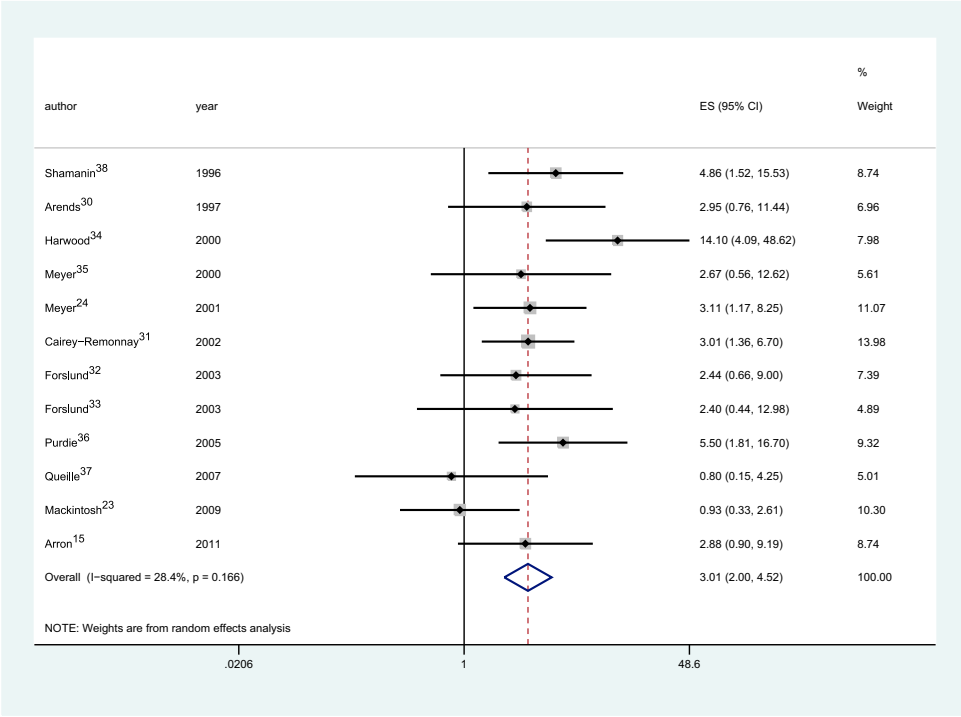

Fig 4. Pooled effect size and 95% confidence intervals (*CI*) for immunosuppressed tumors versus immunocompetent tumors (hypothesis 2), showing that squamous cell carcinoma (SCC) from immunosuppressed patients are more likely to carry human papillomavirus than SCC from immunocompetent patients (pooled ES 3.01, 95% CI 2.00-4.52, P <.0001). I^2 and Q statistics showed minimal evidence of heterogeneity (I^2 = 28.4%, Q = 15.37 [d.f. = 11], P = .17). *EV*, Epidermodysplasia verruciformis.

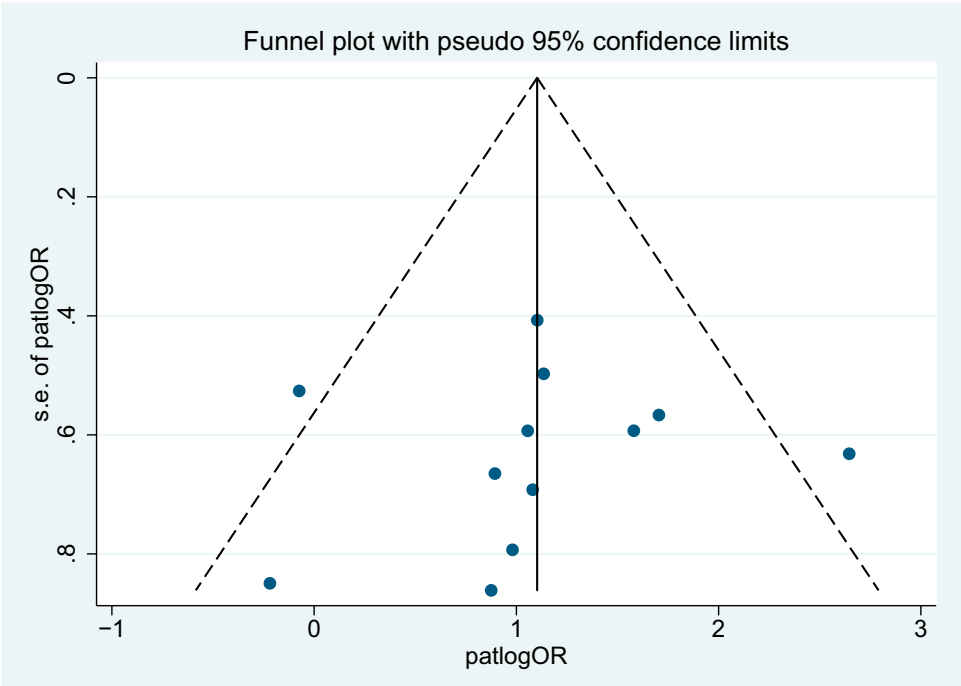

Fig 5. Funnel plot with pseudo 95% confidence intervals for immunosuppressed tumors versus immunocompetent tumors (hypothesis 2) showing no evidence of publication bias (Egger P = .78). *OR*, Odds ratio.

accounting for its presence in only a fraction of the total SCCs.

HPV may act as a co-carcinogen with other factors to amplify the risk of developing cuSCC. In patients with epidermodysplasia verruciformis, SCC develops on sun-exposed skin. Studies have shown that HPV DNA is more prevalent in sun-exposed versus sun-protected skin, also suggesting a link between the 2 factors.[16] HPV could disturb cellular DNA repair or apoptosis mechanisms lending the cells more susceptible to UV-induced damage. Conversely, UV light may have a transient immunosuppressive effect on skin allowing HPV to evade the immune system. Lastly, it has been postulated that HPV may be merely an innocent bystander and is not a factor in the pathogenesis of cuSCC.[40] It may be merely a marker of immunosuppression and a cofounder in the analysis.

Establishing a link between HPV and SCC may have diagnostic and/or therapeutic implications. For example, understanding the mechanism by which Kaposi sarcoma (KS) oncogenesis occurs has allowed for better targeting of treatments toward the human herpesvirus (HHV-8) genome and signaling pathway. Furthermore, the clear relationship between HPV infection and cervical cancer has led to the development of an effective HPV vaccine. HPV vaccines have been shown to be effective against the development of cervical cancer, by producing antibodies that neutralize the virus and prevent HPV infection.[41] If HPV is shown to be involved in a subset of tumors then early vaccination against the offending subtypes may prove of benefit before advance tumor burden or before iatrogenic immunosuppression.

Further research focusing on the natural history of the HPV-induced tumors and their responsiveness to different treatment modalities may be of therapeutic benefit. The case may be similar to head and neck, penile, and vulvar SCC in that HPV association predicts better prognosis or response to therapy. On the contrary, in the skin, HPV-induced tumors may require more aggressive treatment given the immunosuppressed hosts. Longitudinal studies of UV exposure, viral load, specific HPV types in patients, and the subsequent development of SCC would be beneficial. Elucidation of the mechanism in cuSCC may lead to more targeted treatment modalities, reduction of disease burden, and better patient outcomes.

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