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Association Between β-Genus Human Papillomavirus and Cutaneous Squamous Cell Carcinoma in Immunocompetent Individuals—A Meta-analysis

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Abstract

IMPORTANCE

Existing epidemiological evidence remains controversial regarding the association between β-genus human papillomavirus (β-HPV) and cutaneous squamous cell carcinoma (cSCC) in immunocompetent individuals.

OBJECTIVE

We aimed to clarify this association and evaluate type-specific β-HPV involvement.

DATA SOURCES

We performed a systematic literature search of MEDLINE and EMBASE for studies in humans through June 18, 2014, with no restriction on publication date or language. The following search terms were used: "human papillomavirus" and "cutaneous squamous cell carcinoma or skin squamous cell carcinoma or cSCC or nonmelanoma skin neoplasms."

STUDY SELECTION

Articles were independently assessed by 2 reviewers. We only included case-control or cohort studies, in immunocompetent individuals, that calculated the odds ratio (OR) for cSCC associated with overall and type-specific β-HPV.

DATA EXTRACTION AND SYNTHESIS

We first assessed the heterogeneity among study-specific ORs using the Q statistic and I 2 statistic. Then, we used the random-effects model to obtain the overall OR and its 95% CI for all studies as well as for each type of HPV. We also tested and corrected for publication bias by 3 funnel plot–based methods. The quality of each study was assessed with the Newcastle Ottawa Scale.

MAIN OUTCOMES AND MEASURES

Pooled ORs and 95% CIs for overall β-HPV and HPV types 5, 8, 15, 17, 20, 24, 36, and 38 association with skin biopsy proven cSCC. RESULTS Seventy-nine articles were assessed for eligibility; 14 studies met inclusion criteria for the meta-analysis and included 3112 adult immunocompetent study participants with cSCC and 6020 controls. For all detection methods, the overall association between β-HPV and cSCC was significant with an adjusted pooled OR (95% CI) of 1.42 (1.18-1.72). As for the type-specific analysis, types 5, 8, 15, 17, 20, 24, 36, and 38 showed a significant association with adjusted pooled ORs (95% CIs) of 1.4 (1.18-1.66), 1.39 (1.16-1.66), 1.25 (1.04-1.50), 1.34 (1.19-1.52), 1.38 (1.21-1.59), 1.26 (1.09-1.44), 1.23 (1.01-1.50), and 1.37 (1.13-1.67) respectively. Our subgroup analysis in studies using only serology for HPV detection showed a significant association between overall β-HPV and HPV subtypes 5, 8, 17, 20, 24, and 38 with an increased risk of cSCC development.

CONCLUSIONS AND RELEVANCE

This study serves as added evidence supporting β-HPV as a risk factor for cSCC in healthy individuals. The subgroup analysis highlights this significant association for HPV 5, 8, 17, 20, and 38, which may help to direct future prevention efforts

Keywords
Papillomavirus, Carcinoma, Immunocompetent

Comments
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Association Between β-Genus Human Papillomavirus and Cutaneous Squamous Cell Carcinoma in Immunocompetent Individuals—A Meta-analysis

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IMPORTANCE Existing epidemiological evidence remains controversial regarding the association between β-genus human papillomavirus (β-HPV) and cutaneous squamous cell carcinoma (cSCC) in immunocompetent individuals.

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DATA EXTRACTION AND SYNTHESIS We first assessed the heterogeneity among study-specific ORs using the Q statistic and I^2 statistic. Then, we used the random-effects model to obtain the overall OR and its 95% CI for all studies as well as for each type of HPV. We also tested and corrected for publication bias by 3 funnel plot–based methods. The quality of each study was assessed with the Newcastle Ottawa Scale.

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Supplemental content

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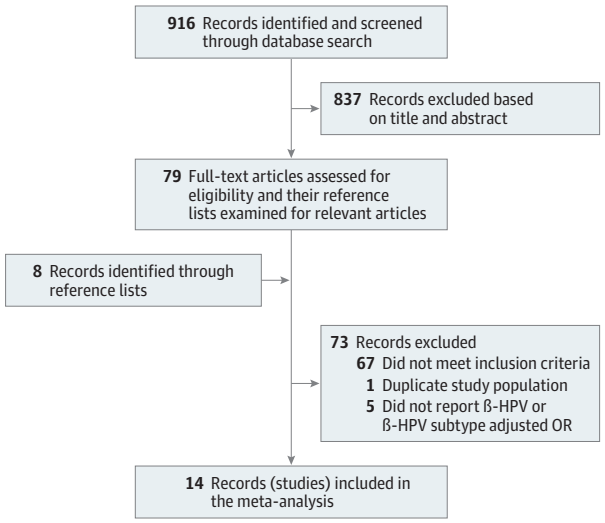
Cutaneous squamous cell carcinoma (cSCC) is one of the most common cancers in men and women worldwide, with more than 700 000 newly diagnosed cases yearly in the United States alone, compared with less than 15 000 newly diagnosed cases yearly of cervical cancer.[1,2] The annual incidence of cSCC has increased at an alarming rate in the last 3 decades, with around 8000 attributable deaths yearly, twice the death rate from invasive cervical cancer. Furthermore, the estimated annual cost of treating cSCC cases in the United States is about $3.8 billion. This highlights the important public health burden that cSCC places on our health care system.[3,4] Therefore, a deeper understanding of cSCC's risk factors should help us to develop more effective preventive measures, in turn decreasing the number of newly diagnosed cases and the financial burden.

The known risk factors implicated in the development of cSCC are UV radiation exposure, immunosuppression, and fair skin.[5] In the context of the recent increase in the rates of newly diagnosed cSCC, a viral etiology has been hypothesized, with human papillomavirus (HPV) being the major incriminated virus.[6-8] Human papillomaviruses are a large and diverse group of more than 170 subtypes with 5 major HPV genera: α papillomavirus, β papillomavirus, γ papillomavirus, μ papillomavirus and ν papillomavirus.[9,10] β-Genus HPV (β-HPV) is the most detected genus in cancerous, precancerous, and normal keratinocytes. The analysis of human papillomatous skin lesions and their relationship to virus infections and carcinogenesis had a slow start because they were considered a cosmetic problem with no significant medical implications. This view gradually changed after 1922, when Lewandowsky and Lutz described a hereditary condition characterized by an extensive verrucosis, called epidermodysplasia verruciformis (EV). The first description of β-HPV infection and cutaneous carcinoma was mainly the work of Stefania Jablonska, who pointed out the potential role of HPV 5 and 8 in these warts as causal factors for the subsequent development of cSCC.[11,12] This later led the International Agency of Research on Cancer (IARC) to consider β-HPV types 5 and 8, found in 90% of cSCC lesions of EV cases, as possibly carcinogenic. Also, the increased occurrence of cSCC in solid organ transplant recipients has been associated with significantly higher rates of β-HPV.[13,14] More recently, the association of β-HPV and cSCC in immunocompetent individuals was evaluated in multiple epidemiological case-control studies[6,8] with controversial results.

The molecular pathways explaining β-HPV's implication in the carcinogenesis of cSCC are not yet fully clarified and could be explained by a number of mechanisms of action, including the following 3 pathways: (1) Increased susceptibility to UV-induced oncogenesis in transgenic mice expressing HPV type 38 E6 and E7 oncoproteins[15-17]; (2) HPV type 8 E6 oncoprotein's capacities to inhibit the PDZ (Psd95-DlgA-ZO1) domain protein syntenin-2, a critical element in the control of viral oncogenic potential (the downstream pathway for syntenin-2 remains to be fully understood)[18,19]; and (3) β-HPV types 5, 8, 20, and 38 through E2, 6, and 7 oncoprotein increase the quantity of stem cell–like cells available during early carcinogenesis, thus enabling the persistence and accumulation of DNA damage necessary to generate malignant stem cells.

Figure 1. Flow Diagram of Systematic Literature Search for the Meta-analysis



β-HPV indicates β human papillomavirus; OR, odds ratio.

These pathways are only a few of the many plausible molecular mechanisms for type-specific β-HPV involvement in the initiation and progression of the onocogenic process in cSCC. However, type-specific β-HPV epidemiological evidence remains controversial. Thus, the primary endpoint of this meta-analysis is to evaluate the existing epidemiological data on type-specific β-HPV association with cSCC in immunocompetent individuals.

Methods

Databases and Search Strategy

We systematically searched for studies in humans through June 18, 2014, with no language restrictions or specified start date. We searched the MEDLINE and EMBASE databases using the following search terms: "human papillomavirus or HPV or β-HPV" and "cutaneous squamous cell carcinoma or skin squamous cell carcinoma or cSCC or nonmelanoma skin neoplasms." The initial inquiry was conducted by one of us (J.C.) and independently verified by the university medical reference librarian. In addition, to ensure comprehensiveness, we examined the reference lists from retrieved articles for supplementary relevant studies. The results were uploaded to Mendeley, a citation database program for review and selection.

Eligibility Criteria

Eligibility was restricted to studies, with human immunocompetent participants only, that examined the association between HPV and cSCC development as primary episode. Studies were excluded if their outcome of interest was the development of melanoma, cutaneous basal cell carcinoma, anogenital cSCC, or recurrent cSCC. As for study design, case-controls and cohorts of at least 40 patients were eligible for inclusion, while we excluded abstracts, letters to the editor, case

Table. Characteristics of Studies Meeting Search Inclusion Criteria

Source	Design and Population	Multicenter/ Latitude	β-HPV Detection Methods/ Subtypes	Newcastle-Ottawa Score/ Adjustment
Masini et al,[20] 2003	Case-control Cases: 46 Controls: 84	No/41.54° N	ELISA serology HPV types 8,15, 36	7 Adjusted for age, sex, eye color, and history of lifetime exposure to sunlight
Feltkamp et al,[11] 2003	Case-control Cases: 161 Controls: 386	No/52.16° N	ELISA serology HPV types 5, 8, 15, 20, 24, 38	6 Adjusted for age and sex
Karagas et al,[21] 2006	Case-control Cases: 252 Control: 461	No/44° N	Multiplex serology HPV types 5, 8, 15, 20, 24, 36, 38 and overall β-HPV	9 Adjusted for age, sex, and skin sensitivity
Casabonne et al,[22] 2007	Case-control Cases: 39 Controls: 80	No/51.7° N	Multiplex serology HPV types 5, 8, 15, 17, 20, 24, 36, 38	8 Adjusted for age, sex, and region of residence
Waterboer et al,[23] 2008	Case-control Cases: 43 Controls: 77	No/41.54° N	Multiplex serology HPV types 5, 8, 15, 17, 20, 24, 36, 38, and overall β-HPV	8 Adjusted for age, sex, eye color, and history of lifetime sun exposure
Bouwes Bavinck et al,[24] 2010	Case-control Cases: 689 Controls: 845	Yes/NA	Multiplex serology HPV types: 5, 8, 15, 17, 20, 24, 36, 38 EBH DNA by PCR HPV types: 5, 8, 20, 24, 36	9 Adjusted for age and sex
Karagas et al,[25] 2010	Case-control Cases: 663 Controls: 805	No/40° N	Multiplex serology HPV types 5, 8, 15, 17, 20, 24, 36, 38, and overall β-HPV	9 Adjusted for age, sex, level of education, cigarette smoking, skin sensitivity, and number of lifetime painful sunburns
Plasmeijer et al,[26] 2011	Cohort: 1311 cSCC newly diagnosed: 150	No/26° S	Multiplex serology HPV types 5, 8, 15, 20, 24, 36, 38, and overall β-HPV	8 Adjusted for age and sex; used Cox proportional hazards
Andersson et al,[27] 2012	Cohort: 850 000 Cases: 633 Controls: 633	Yes/60° N	Multiplex serology HPV types 5, 8, 15, 17, 20, 24, 36, 38 and overall β-HPV	9 Adjusted age, sex and country
Struijk et al,[28] 2006	Case-control Cases: 64 Controls: 57	No/26° S	ELISA Serology: HPV types 8, 15, 24 and overall β-HPV EBH DNA by PCR: HPV types 5, 8, 15, 20, 24, 36, 38 and overall β-HPV	7 Adjusted for age and sex
Iannacone et al,[29] 2012	Case-control Cases: 173 Controls: 300	No/28° N	Multiplex serology HPV types 5, 8, 15, 17, 20, 24, 36, 38 and overall β-HPV	8 Adjusted for age and sex
Struijk et al,[30] 2003	Case-control Case: 155 Control: 371	No/52.16° N	EBH DNA by PCR HPV types 5, 8, 15, 20, 24, 38	7 Adjusted for age and sex
Termorshuizen et al,[31] 2004	Case-control Cases: 156 Controls: 320	No/52.16° N	ELISA serology HPV types 5, 8, 15, 20 EBH DNA by PCR: HPV types 5, 8, 15, 20	6 Adjusted for age and sex
Iannacone et al,[32] 2014	Case-control Cases: 168 Controls: 290	No/28° N	EBH DNA by PCR HPV types 5, 8, 15, 20, 24, 36, 38 and overall β-HPV	8 Adjusted for age, sex, education, hair color sunlight exposure, tanning ability, and ever-smoking status

Abbreviations: β-HPV indicates β human papillomavirus; EBH, eyebrow hair.

reports, review articles, case-controls (<20 cases and <20 controls), and cohort studies (<40 patients). Studies including less than 40 patients were excluded, because they lacked statistically significant power. Furthermore, studies not reporting the associated risk for at least 2 of the HPV subtypes 5, 8, 15, 17, 20, 24, 36, and 38 were excluded from the analysis. To be included in our analysis, studies had to report type-specific β-HPV odds ratio (OR) or relative risk (RR) with 95% CIs. Restrictions were not placed on the method of detection of HPV.

Selection Process

Two of us (J.C.) and (A.S.) independently reviewed the titles and abstracts of the previously searched databases. Based on the prespecified selection criteria, both authors independently identified studies. Disagreements were resolved by discussion with a prior agreement that any unsettled conflict would be determined by a third author (A.G.R.).

Data collection forms were used by both authors to extract the required data from eligible studies. Then both authors assessed extracted studies for duplication by comparing authors' names, dates of publication, and population sizes. Both authors were unblinded to the studies' authors' names, population sizes, journals of publication, and locations.

Data Extraction

Primary outcome measures were ORs with the corresponding 95% CIs for the association of β-HPV and primary episodes of cSCC. We identified the ORs reflecting the greatest degree of adjustment for possible confounding factors. The adjusted ORs with 95% CIs for overall β-HPV, HPV types 5, 8, 15, 17, 20, 24, 36, and 38 were extracted, when applicable. Other data of interest included study general information: first author name, year of publication, location, and estimated latitude where the study population was enrolled. Information on

study design, population size and characteristics, the method of HPV detection, and the number of β-HPV subtypes analyzed was also collected. In certain circumstances when required data were not reported, authors corresponded with study authors via email.

Assessment of Bias Risk

Two of us (A.S. and J.C.) independently used the Newcastle-Ottawa Scale (NOS) for assessing the individual quality of each study. We used ORs to approximate RR given the rare disease assumption. We first assessed the heterogeneity among study-specific ORs using the Q statistic and I^2 statistic. We also tested and corrected for publication bias by 3 funnel plot–based methods: the Egger test, the Begg test, and the trim & fill method.

Statistical Analysis

The meta-analysis was performed on qualifying studies that had reported adjusted ORs of the association between global and type-specific β-HPV with cSCC regardless of the detection method. As for the subgroup analyses, they were restricted to studies using seroprevalence detected by multiplex serology or enzyme-linked immunosorbent assay (ELISA). The adjusted ORs with 95% CIs were identified based on the meta-analysis results. Random-effects method was used to pool the ORs and 95% CIs. All study analyses were performed using the R (R Development Core Team, 2008) and metafor package (Wolfgang Viechtbauer, 2010).

Results

Study Screening

The literature search of the MEDLINE and EMBASE databases yielded 916 articles. After review of the titles and abstracts, 837 articles were excluded for lack of adherence to our inclusion criteria. We reviewed the full text of the selected 79 articles and assessed their reference lists for relevant publications, retrieving 8 additional publications. Based on this review, we excluded 67 publications for nonadherence with the inclusion criteria. Furthermore, 1 publication was excluded for data overlap with another study, and we included the one with the highest adjustment for OR in the meta-analysis. We also excluded 5 publications for not providing the associated risk of β-HPV subtypes, based on our correspondence with the authors. The flow diagram of the systematic literature review is illustrated in **Figure 1**.

Study Characteristics

The studies included in our meta-analysis comprised 12 case-control studies and 2 cohort studies (**Table**).[11,20-32] Publication years ranged from 2003 to 2014, with data collected from as late as 1992. All studies included adult immunocompetent participants, males and females of all ages, a total of 3112 cases and 6020 controls. Our subgroup analysis comprised 12 studies that exclusively used serology as the HPV detection method and included 2789 cases and 5359 controls. Because UV light exposure is a major risk factor for cSCC and has been implicated as a cofactor with β-HPV in the initiation of carcinogenesis in multiple molecular models, we evaluated the latitude of each study region.[33] We determined that 11 studies were conducted in the northern hemisphere between estimated latitudes 40° N to 60° N, while only 2 studies were conducted in the southern hemisphere at an estimated latitude of 26° S. All included studies assessed cSCC as primary outcome in both controls and cases by skin biopsy pathological evaluation. All 14 studies adjusted for age and sex when calculating the β-HPV and cSCC associated ORs. Only 8 studies also adjusted for 1 or more of the following: skin sensitivity, region of residence, eye color, number of lifetime painful sun burns, smoking history, or lifetime exposure to sunlight. The most used detection technique for different types of HPV was serology by multiplex polymerase chain reaction (PCR) (8 studies); the ELISA assay was used in 4 studies and eyebrow hair DNA in 5 studies. ELISA serology is a less sensitive and specific method, compared with multiplex serology, and was used only in studies published between 2003 and 2006 when multiplex serology was not readily available. Serology is a highly cost-effective HPV detection method, because it allows for large-scale studies as well as tracking a population over time for analyses in HPV infections. Previous studies[32,34] have shown acceptable comparability in sensitivity between β-HPV collected by eyebrow hair, serology, and surgical biopsy. The selection of the β-HPV subtypes included in both our meta-analysis and subgroup analysis was based on the number of studies evaluating each subtype: β-HPV 8 and 15 (13 studies); β-HPV 5, 20, 24, and 38 (12 studies); β-HPV 36 (10 studies); and β-HPV 17 (7 studies). HPV type 17 is one subtype of interest that was not evaluated in most studies. Additional information and extracted data from the included studies are presented in eTable 1 in the Supplement.

Study Quality

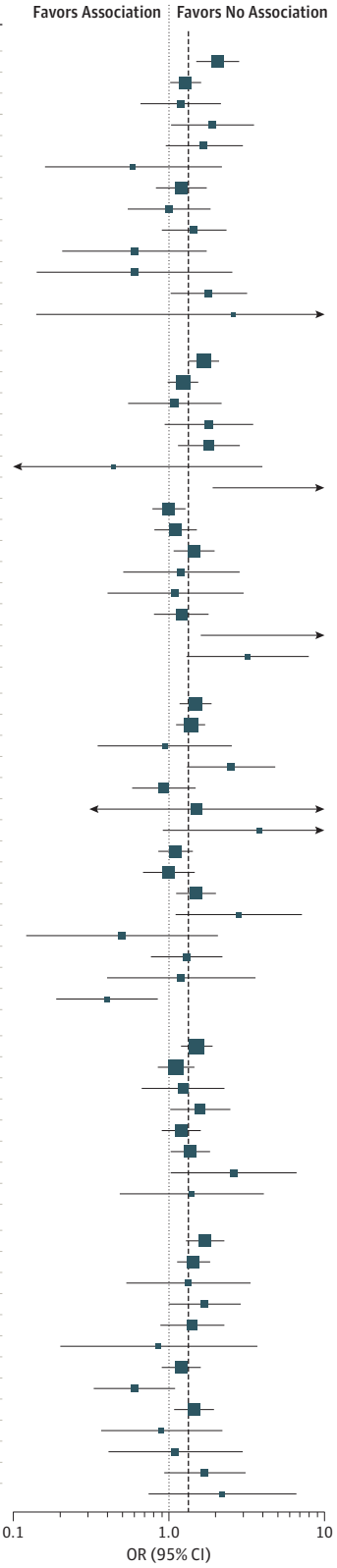
Quality assessment was performed using the Newcastle Ottawa scale, which is specifically used for nonrandomized studies and has been endorsed by the Cochrane collaboration. We adequately used the version for case-control studies or cohort studies as applicable, addressing subject selection, study comparability, and the assessment of outcome or exposure. NOS scores from 6 to 9 (9 being the highest possible score), with a mean of 7.8, median and mode of 8. All studies earned a star for comparability with regard to age and sex adjustment. Eight studies received an additional star for comparability, because they also adjusted for skin sensitivity, region of residence, or lifetime exposure to sunlight. A summary of the included study evaluation as assessed using the NOS is shown eTable 2 in the Supplement.

Publication Bias

Publication bias was not detected for the pooled studies, or the subgroup analysis studies using the Egger test[35] and the Begg test.[36] We also conducted sensitivity analyses on both the pooled studies and the subgroup data sets to evaluate the potential impact of publication bias on the conclusions. We specifically applied the trim and fill method to evaluate the subgroup analysis data set and imputed 5 studies.[37] The corrected ORs remained similar to the uncorrected ones, suggesting that the impact of the publication bias for this subgroup is small.

Figure 2. Forest Plot for the Studies on the Association of HPV 5, 8, 15, 17, and 20 With cSCC

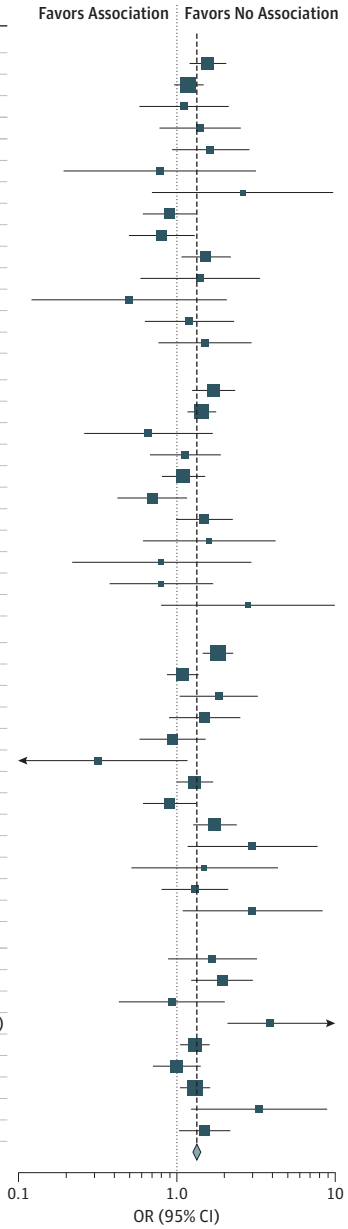
Study, year	Cases/Controls, No.	Positive, %	RR (95% CI)
HPV-5 (I^2: 25%)			1.40 (1.18-1.66)
Bouwes Bavinck et al,[24] 2010	645/807	16.90/9.05	2.05 (1.49-2.82)
Bouwes Bavinck et al,[24] 2010	675/829	29.04/24.25	1.28 (1.02-1.61)
Iannacone et al,[32] 2014	168/290	24.40/17.24	1.19 (0.66-2.15)
Struijk et al,[30] 2003	81/212	44.44/22.17	1.90 (1.03-3.50)
Iannacone et al,[29] 2012	173/300	20.23/12.67	1.68 (0.95-2.97)
Struijk et al,[28] 2006	43/45	18.60/24.44	0.59 (0.16-2.19)
Andersson et al,[27] 2012	633/NA	10.74/NA	1.20 (0.82-1.75)
Plasmeijer et al,[26] 2011	150/NA	9.33/NA	1.00 (0.54-1.84)
Karagas et al,[25] 2010	663/805	6.49/5.09	1.45 (0.90-2.34)
Waterboer et al,[23] 2008	43/77	27.91/28.57	0.60 (0.21-1.75)
Casabonne et al,[22] 2007	39/80	12.82/20.00	0.60 (0.14-2.55)
Karagas et al,[21] 2006	252/461	11.11/6.72	1.80 (1.02-3.17)
Feltkamp et al,[11] 2003	160/333	1.25/0.30	2.60 (0.21-32.83)
HPV-8 (I^2: 53%)			1.39 (1.16-1.66)
Bouwes Bavinck et al,[24] 2010	645/807	39.53/28.00	1.68 (1.35-2.10)
Bouwes Bavinck et al,[24] 2010	675/829	28.44/24.37	1.23 (0.98-1.55)
Iannacone et al,[32] 2014	168/290	17.26/12.07	1.09 (0.55-2.17)
Struijk et al,[30] 2003	72/203	37.50/18.72	1.80 (0.94-3.46)
Iannacone et al,[29] 2012	173/300	36.42/23.00	1.80 (1.14-2.84)
Struijk et al,[28] 2006	37/36	5.41/5.56	0.44 (0.05-3.98)
Struijk et al,[28] 2006	47/46	29.79/4.35	9.30 (1.90-45.56)
Andersson et al,[27] 2012	633/NA	23.70/NA	1.00 (0.78-1.27)
Plasmeijer et al,[26] 2011	150/NA	36.67/NA	1.10 (0.80-1.51)
Karagas et al,[25] 2010	663/805	19.16/15.28	1.45 (1.07-1.96)
Waterboer et al,[23] 2008	43/77	37.21/16.88	1.20 (0.51-2.84)
Casabonne et al,[22] 2007	39/80	23.08/20.00	1.10 (0.40-3.01)
Karagas et al,[21] 2006	252/461	16.27/14.75	1.20 (0.80-1.80)
Feltkamp et al,[11] 2003	160/333	4.38/0.30	14.70 (1.60-135.02)
Masini et al,[20] 2003	46/84	56.52/32.14	3.20 (1.30-7.89)
HPV-15 (I^2: 50%)			1.25 (1.04-1.50)
Bouwes Bavinck et al,[24] 2010	645/807	30.39/22.80	1.48 (1.17-1.87)
Bouwes Bavinck et al,[24] 2010	675/829	37.04/29.92	1.38 (1.11-1.71)
Iannacone et al,[32] 2014	168/290	5.95/5.86	0.94 (0.35-2.54)
Struijk et al,[30] 2003	71/195	36.62/15.38	2.50 (1.30-4.80)
Iannacone et al,[29] 2012	173/300	28.90/25.33	0.93 (0.58-1.49)
Struijk et al,[28] 2006	36/35	2.78/2.86	0.64 (0.04-10.61)
Struijk et al,[28] 2006	43/47	23.26/6.38	3.80 (0.91-15.83)
Andersson et al,[27] 2012	633/NA	20.70/NA	1.10 (0.85-1.42)
Plasmeijer et al,[26] 2011	150/NA	25.33/NA	1.00 (0.68-1.46)
Karagas et al,[25] 2010	663/805	22.02/16.65	1.49 (1.11-2.00)
Waterboer et al,[23] 2008	43/77	41.86/24.68	2.80 (1.10-7.11)
Casabonne et al,[22] 2007	39/80	10.26/18.75	0.50 (0.12-2.06)
Karagas et al,[21] 2006	252/461	10.32/8.89	1.30 (0.77-2.20)
Feltkamp et al,[11] 2003	160/333	4.38/2.10	1.20 (0.40-3.60)
Masini et al,[20] 2003	79/84	62.03/47.62	0.40 (0.19-0.85)
HPV-17 (I^2: 0%)			1.34 (1.19-1.52)
Bouwes Bavinck et al,[24] 2010	645/807	31.78/23.54	1.51 (1.20-1.91)
Bouwes Bavinck et al,[24] 2010	675/829	17.33/15.92	1.11 (0.84-1.46)
Iannacone et al,[32] 2014	168/290	22.02/14.48	1.23 (0.67-2.26)
Iannacone et al,[29] 2012	173/300	35.26/25.67	1.59 (1.02-2.48)
Andersson et al,[27] 2012	633/NA	23.06/NA	1.20 (0.90-1.60)
Karagas et al,[21] 2006	663/805	20.21/16.40	1.37 (1.02-1.84)
Waterboer et al,[23] 2008	43/77	46.51/27.27	2.60 (1.02-6.60)
Casabonne et al,[22] 2007	39/80	20.51/15.00	1.40 (0.48-4.06)
HPV-20 (I^2: 14%)			1.38 (1.21-1.59)
Bouwes Bavinck et al,[24] 2010	645/807	20.00/12.76	1.71 (1.29-2.27)
Bouwes Bavinck et al,[24] 2010	675/829	26.37/19.9	1.44 (1.13-1.84)
Iannacone et al,[32] 2014	168/290	8.33/6.21	1.33 (0.53-3.33)
Struijk et al,[30] 2003	96/254	53.12/35.04	1.70 (1.00-2.89)
Iannacone et al,[29] 2012	173/300	29.48/21.00	1.41 (0.88-2.26)
Struijk et al,[28] 2006	46/40	23.91/15.00	0.86 (0.20-3.70)
Andersson et al,[27] 2012	633/NA	20.70/NA	1.20 (0.90-1.60)
Plasmeijer et al,[26] 2011	150/NA	11.33/NA	0.60 (0.33-1.10)
Karagas et al,[25] 2010	663/805	19.76/15.16	1.45 (1.08-1.95)
Waterboer et al,[23] 2008	43/77	30.23/29.87	0.90 (0.37-2.20)
Casabonne et al,[22] 2007	39/80	23.08/21.25	1.10 (0.41-2.96)
Karagas et al,[21] 2006	252/461	9.92/6.07	1.70 (0.93-3.10)
Feltkamp et al,[11] 2003	160/333	5.00/2.10	2.20 (0.74-6.58)



The squares and horizontal lines correspond to the study-specific odds ratios (ORs) and 95% CIs. The diamond represents the pooled OR and 95% CI of the overall population. The vertical dashed line indicates the overall pooled OR of 1.33. cSCC, cutaneous squamous cell carcinoma; HPV, human papillomavirus; NA, not available; OR, odds ratio; RR, relative risk.

Figure 3. Forest Plot for Studies on the Association Between HPV 24, 36, and 38, and β-HPV and cSCC

Study, year	Cases/Controls No.	Positive, %	RR (95% CI)
HPV-24 (I^2: 14%)			1.26 (1.09-1.44)
Bouwes Bavinck et al,[24] 2010	645/807	22.02/15.24	1.57 (1.20-2.05)
Bouwes Bavinck et al,[24] 2010	675/829	36.59/32.69	1.19 (0.96-1.47)
Iannacone et al,[32] 2014	168/290	20.83/12.76	1.11 (0.58-2.12)
Struijk et al,[30] 2003	84/221	46.43/25.34	1.40 (0.78-2.52)
Iannacone et al,[29] 2012	173/300	20.81/12.33	1.63 (0.93-2.86)
Struijk et al,[28] 2006	44/41	20.45/17.07	0.78 (0.19-3.15)
Struijk et al,[28] 2006	41/48	19.51/8.33	2.60 (0.70-9.68)
Andersson et al,[27] 2012	633/NA	10.43/NA	0.90 (0.61-1.32)
Plasmeijer et al,[26] 2011	150/NA	14.67/NA	0.80 (0.50-1.29)
Karagas et al,[25] 2010	663/805	12.67/10.06	1.53 (1.07-2.18)
Waterboer et al,[23] 2008	43/77	37.21/27.27	1.40 (0.59-3.33)
Casabonne et al,[22] 2007	39/80	12.82/20.00	0.50 (0.12-2.06)
Karagas et al,[21] 2006	252/461	7.14/6.29	1.20 (0.63-2.30)
Feltkamp et al,[11] 2003	160/333	13.12/6.61	1.50 (0.76-2.95)
HPV-36 (I^2: 42%)			1.23 (1.01-1.50)
Bouwes Bavinck et al,[24] 2010	645/807	15.81/9.91	1.71 (1.25-2.34)
Bouwes Bavinck et al,[24] 2010	675/829	41.78/33.29	1.44 (1.17-1.77)
Iannacone et al,[32] 2014	168/290	6.55/7.59	0.66 (0.26-1.68)
Iannacone et al,[29] 2012	173/300	23.12/17.33	1.13 (0.68-1.89)
Andersson et al,[27] 2012	633/NA	12.95/NA	1.10 (0.80-1.51)
Plasmeijer et al,[26] 2011	150/NA	10.67/NA	0.70 (0.42-1.16)
Karagas et al,[25] 2010	633/805	8.90/7.20	1.49 (0.99-2.25)
Waterboer et al,[23] 2008	43/77	32.56/24.68	1.60 (0.61-4.18)
Casabonne et al,[22] 2007	39/80	15.38/16.25	0.80 (0.22-2.94)
Karagas et al,[21] 2006	252/461	4.37/5.64	0.80 (0.38-1.70)
Masini et al,[20] 2003	46/84	19.57/8.33	2.80 (0.79-9.90)
HPV-38 (I^2: 60%)			1.37 (1.13-1.67)
Bouwes Bavinck et al,[24] 2010	645/807	37.67/24.91	1.82 (1.46-2.27)
Bouwes Bavinck et al,[24] 2010	675/829	27.70/26.06	1.09 (0.87-1.37)
Iannacone et al,[32] 2014	168/290	32.74/17.93	1.84 (1.04-3.25)
Struijk et al,[30] 2003	95/256	52.63/35.55	1.50 (0.89-2.52)
Iannacone et al,[29] 2012	173/300	24.28/24.67	0.94 (0.58-1.52)
Struijk et al,[28] 2006	43/49	18.60/30.61	0.32 (0.09-1.17)
Andersson et al,[27] 2012	633/NA	20.54/NA	1.30 (1.00-1.69)
Plasmeijer et al,[26] 2011	150/NA	32.00/NA	0.90 (0.61-1.32)
Karagas et al,[25] 2010	663/805	18.70/12.05	1.74 (1.27-2.39)
Waterboer et al,[23] 2008	43/77	48.84/27.27	3.00 (1.17-7.70)
Casabonne et al,[22] 2007	39/80	25.64/17.50	1.50 (0.52-4.35)
Karagas et al,[21] 2006	252/461	13.49/10.85	1.30 (0.80-2.11)
Feltkamp et al,[11] 2003	160/333	5.62/2.70	3.00 (1.09-8.29)
HPV-genus β (I^2: 45%)			1.42 (1.18-1.72)
Iannacone et al,[32] 2014	168/290	86.90/73.45	1.68 (0.88-3.20)
Iannacone et al,[29] 2012	173/300	73.41/60.33	1.93 (1.23-3.02)
Struijk et al,[28] 2006	63/57	44.44/40.35	0.93 (0.43-2.01)
Struijk et al,[28] 2006	54/52	37.04/13.46	3.90 (1.41-10.78)
Andersson et al,[27] 2012	NA/NA	NA/NA	1.30 (1.05-1.62)
Plasmeijer et al,[26] 2011	150/NA	70.67/NA	1.00 (0.71-1.41)
Karagas et al,[25] 2010	663/805	53.09/45.84	1.30 (1.04-1.62)
Waterboer et al,[23] 2008	NA/NA	NA/NA	3.30 (1.23-8.89)
Karagas et al,[21] 2006	252/461	32.54/24.73	1.50 (1.04-2.17)
Random-effects model using DerSimonian-Laird			1.33 (1.26-1.41)



The squares and horizontal lines correspond to the study-specific odds ratios (ORs) and 95% CIs. The diamond represents the pooled OR and 95% CI of the overall population. The vertical dashed line indicates the overall pooled OR of 1.33. cSCC, cutaneous squamous cell carcinoma; HPV, human papillomavirus; NA, not available; OR, odds ratio; RR, relative risk.

Meta-analysis

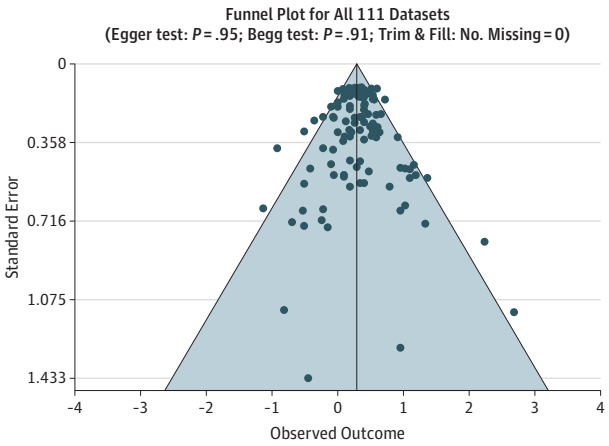
Type-Specific β-HPV Association With cSCC

Our meta-analysis comprised a total of 14 studies (3112 cases; 6020 controls). In the pooled analysis, overall β-HPV-cSCC association was significant with an adjusted pooled OR of 1.4 (95% CI, 1.2-1.7). For the type-specific analysis, types 5, 8, 15, 17, 20, 24, 36, and 38 showed a significant association with adjusted pooled ORs of 1.4 (95% CI, 1.2-1.7), 1.4 (95% CI, 1.2-1.7), 1.2 (95% CI, 1.0-1.5), 1.3 (95% CI, 1.2-1.5), 1.4 (95% CI, 1.2-1.6), 1.3 (95% CI, 1.1-1,4), 1.2 (95% CI, 1.0-1.5), and 1.4 (95% CI, 1.1-1.7) respectively (**Figure 2** and **Figure 3**). A random-effects model was used because heterogeneity was identified among the 13 studies. Visual inspection of the funnel plot revealed no publication bias, later confirmed by the Begg adjusted rank correlation test (**Figure 4**). The funnel plots and their respective Begg adjusted rank correlation tests are represented in supplement eFigures 1-9 in the Supplement.

Type-Specific β-HPV Association With cSCC: Seroprevalence Only

Our subgroup meta-analysis comprised a total of 12 studies (2789 cases; 5359 controls). The pooled analysis of the overall β-HPV association with cSCC was significant, with adjusted

Figure 4. Funnel Plot for Studies on the Association Between β-HPV and cSCC



The vertical solid line represents the summary effect estimates, and the dotted lines are pseudo 95% CIs.

pooled ORs of 1.4 (95% CI, 1.2-1.8), an increased associated risk of 45% for cSCC development. In respect to the type-specific pooled analysis, types HPV 5, 8, 17, 20, 24, and 38 were significantly associated with increased risk of cSCC; the adjusted pooled ORs were 1.4 (95% CI, 1.1-1.8), 1.5 (95% CI, 1.2-1.8), 1.4 (95% CI, 1.2-1.6), 1.3 (95% CI, 1.1-1.6), 1.3 (95% CI, 1.0-1.6), and 1.4 (95% CI, 1.1-1.8), respectively. Human papillomavirus 15 and 36 did not show any significant increased risk for cSCC with respective adjusted pooled OR of 1.1 (95% CI, 0.9-1.5) and 1.11 (95% CI, 0.9-1.4) (**Figure 5** and **Figure 6**). Heterogeneity was identified among the 12 studies. The funnel plots and their respective Begg adjusted rank correlation tests are represented in eFigures 10 through 21 in Supplement 2.

Discussion

This pooled analysis included a large data sample of case-control and cohort studies evaluating the association between type-specific β-HPV and cSCC. The findings suggest that β-HPV is associated with a 42% increase in the risk of cSCC among immunocompetent individuals. This analysis highlights specifically types 5, 8, 15, 17, 20, 24, 36, and 38, with an associated increased risk of 40%, 39%, 25%, 34%, 38%, 26%, 23%, and 36%, respectively. Notably, to our knowledge, this study is the largest to evaluate the type-specific β-HPV associated risk of cSCC. Our subgroup analysis showed similar results with the exception of HPV type 15. In concordance with our pooled analysis, Aldabagh et al[7] performed an extensive meta-analysis evaluating the association of cSCC and β-HPV in both immunocompromised and healthy individuals, restricted to biopsy PCR HPV detection, and that suggested an increased risk of cSCC associated with HPV. Their analysis was not restricted to immunocompetent individuals and included only studies using biopsy specimens with PCR-based detection of HPV, with significant evidence of statistical heterogeneity in the included studies. A major source of heterogeneity in their analysis was the inclusion of 10 studies that did not strictly account for cutaneous HPV subtypes. Furthermore, the results did not account for the HPV type-specific associations, which represents another limitation to their findings.

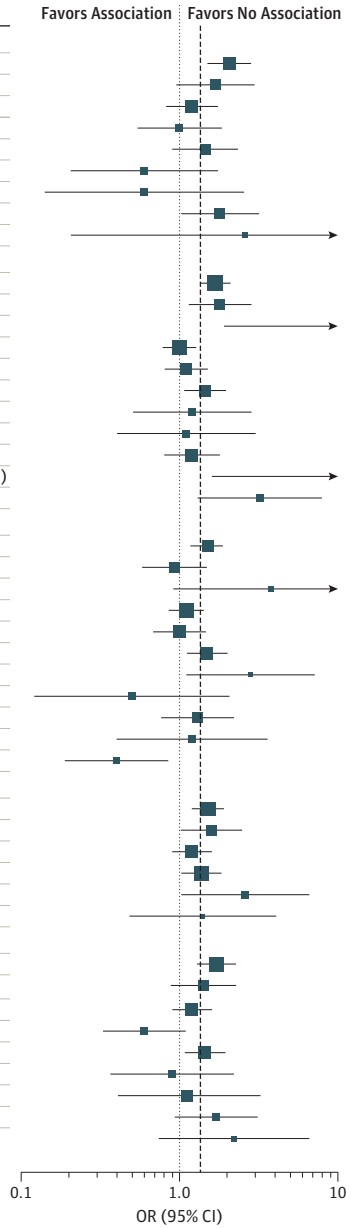
Moreover, a concordance exists between our epidemiological HPV type-specific findings and the established type-specific molecular explanations of HPV mechanism in cSCC carcinogenesis. Specifically, the E6 proteins of HPV 5 and 8 are known to inhibit the transforming growth factor β (TGFβ) signaling pathway through degradation of the SMAD3 transcription factor.[38,39] A pathway that normally plays an essential role in the cell cycle, which could negatively affect viral DNA replication and cell transformation. Also, HPV 5 and 8 E6 proteins induce the recruitment of MAML1, which represses the cutaneous tumor-suppressive Notch signaling pathway, favoring *RAS* oncogene.[40,41] This in turn can upregulate AP1-activating Wnt5a signaling in keratinocytes, a classical skin carcinogenesis pathway.[15,42] Finally, HPV 5 and 8 E6 expression increases the carcinogenic potential of UV-B exposure by promoting p300 degradation, thus increasing thymine dimer persistence and UV-induced double-strand breaks.[18] However, HPV 20 has been shown to upregulate the p16INK4a and Akt-PI3K pathway, interfering with the cell cycle involved in progression to basal cell carcinoma. It is also known that the E6 proteins of HPV 20 can prevent UV-treated keratinocytes from undergoing apoptosis,[15,16,38,43] while HPV38 E7 can degrade pRb increasing the lifespan of human keratinocytes by deregulating the cell cycle.[15,44,45] In addition, the activation of nuclear factor kappa beta is believed to protect β-HPV immortalized human keratinocytes against tumor necrosis factor (TNF) and UV-mediated apoptosis.[46] Among all of the identified HPV types in our pooled analysis, only HPV 17 E7 binds to UBR4, the effect of this interaction contributes to cellular transformation and anchorage independent growth.[41] Interestingly the recent effort by Cohen et al,[47] evaluating *BRAF* induced-cSCC, highlighted HPV 17 as the most frequently isolated genotype. Molecular evidence also supporting the involvement of β-HPV in cSCC carcinogenesis is the recent discovery of the rs7208422 polymorphism in the *EVER2* gene, which was associated with an increased risk of cSCC in healthy individuals who did not have EV.[48] Previously, it was known that the homozygous mutations in *EVER2* genes cause EV, which in turn leads to the development of cSCC associated with β-HPV infections. *EVER2* loss facilitates activation of the HPV 5 long control region through a JNK-dependent pathway facilitating HPV replication and cSCC development.[49]

Quality of the Evidence

This constitutes the most extensive meta-analysis on the topic. Although most of the studies included in our meta-analysis were case-control studies, they were of higher quality, with NOS scores ranging between 6 and 9. We addressed the interstudy heterogeneity, a major limitation of previous research on this topic. First, the statistical tests showed no significant heterogeneity between the included studies in both our meta-analysis and subgroup analysis. Second, to account for the

Figure 5. Forest Plot for the Subgroup Meta-analysis: Seroprevalence Only

Study, year	Cases/Controls No.	Positive, %	RR (95% CI)
HPV-5 (I^2: 33%)			1.43(1.13-1.82)
Bouwes Bavinck et al,[24] 2010	645/807	16.90/9.05	2.05 (1.49-2.82)
Iannacone et al,[29] 2012	173/300	20.23/12.67	1.68 (0.95-2.97)
Andersson et al,[27] 2012	633/NA	10.74/NA	1.20 (0.82-1.75)
Plasmeijer et al,[26] 2011	150/NA	9.33/NA	1.00 (0.54-1.84)
Karagas et al,[25] 2010	663/805	6.49/5.09	1.45 (0.90-2.34)
Waterboer et al,[23] 2008	43/77	27.91/28.57	0.60 (0.21-1.75)
Casabonne et al,[22] 2007	39/80	12.82/20.00	0.60 (0.14-2.55)
Karagas et al,[21] 2006	252/461	11.11/6.72	1.80 (1.02-3.17)
Feltkamp et al,[11] 2003	160/333	1.25/0.30	2.60 (0.21-32.83)
HPV-8 (I^2: 63%)			1.46 (1.16-1.84)
Bouwes Bavinck et al,[24] 2010	645/807	39.53/28.00	1.68 (1.35-2.10)
Iannacone et al,[29] 2012	173/300	36.42/23.00	1.80 (1.14-2.84)
Struijk et al,[28] 2006	47/46	29.79/4.35	9.30 (1.90-45.56)
Andersson et al,[27] 2012	633/NA	23.70/NA	1.00 (0.78-1.27)
Plasmeijer et al,[26] 2011	150/NA	36.67/NA	1.10 (0.80-1.51)
Karagas et al,[25] 2010	663/805	19.16/15.28	1.45 (1.07-1.96)
Waterboer et al,[23] 2008	43/77	37.21/16.88	1.20 (0.51-2.84)
Casabonne et al,[22] 2007	39/80	23.08/20.00	1.10 (0.40-3.01)
Karagas et al,[21] 2006	252/461	16.27/14.75	1.20 (0.80-1.80)
Feltkamp et al,[11] 2003	160/333	4.38/0.30	14.70 (1.60-135.02)
Masini et al,[20] 2003	46/84	56.52/32.14	3.20 (1.30-7.89)
HPV-15 (I^2: 56%)			1.18 (0.95-1.48)
Bouwes Bavinck et al,[24] 2010	645/807	30.39/22.80	1.48 (1.17-1.87)
Iannacone et al,[29] 2012	173/300	28.90/25.33	0.93 (0.58-1.49)
Struijk et al,[28] 2006	43/47	23.26/6.38	3.80 (0.91-15.83)
Andersson et al,[27] 2012	633/NA	20.70/NA	1.10 (0.85-1.42)
Plasmeijer et al,[26] 2011	150/NA	25.33/NA	1.00 (0.68-1.46)
Karagas et al,[25] 2010	663/805	22.02/16.65	1.49 (1.11-2.00)
Waterboer et al,[23] 2008	43/77	41.86/24.68	2.80 (1.10-7.11)
Casabonne et al,[22] 2007	39/80	10.26/18.75	0.50 (0.12-2.06)
Karagas et al,[21] 2006	252/461	10.32/8.89	1.30 (0.77-2.20)
Feltkamp et al,[11] 2003	160/333	4.38/2.10	1.20 (0.40-3.60)
Masini et al,[20] 2003	79/84	62.03/47.62	0.40 (0.19-0.85)
HPV-17 (I^2: 0%)			1.42 (1.23-1.64)
Bouwes Bavinck et al,[24] 2010	645/807	31.78/23.54	1.51 (1.20-1.91)
Iannacone et al,[29] 2012	173/300	35.26/25.67	1.59 (1.02-2.48)
Andersson et al,[27] 2012	633/NA	23.06/NA	1.20 (0.90-1.60)
Karagas et al,[25] 2010	633/805	20.21/16.40	1.37 (1.02-1.84)
Waterboer et al,[23] 2008	43/77	46.51/27.27	2.60 (1.02-6.60)
Casabonne et al,[22] 2007	39/80	20.51/15.00	1.40 (0.48-4.06)
HPV-20 (I^2: 38%)			1.33 (1.08-1.63)
Bouwes Bavinck et al,[24] 2010	645/807	20.00/12.76	1.71 (1.29-2.27)
Iannacone et al,[29] 2012	173/300	29.48/21.00	1.41 (0.88-2.26)
Andersson et al,[27] 2012	633/NA	20.70/NA	1.20 (0.90-1.60)
Plasmeijer et al,[26] 2011	150/NA	11.33/NA	0.60 (0.33-1.10)
Karagas et al,[25] 2010	633/805	19.76/15.16	1.45 (1.08-1.95)
Waterboer et al,[23] 2008	43/77	30.23/29.87	0.90 (0.37-2.20)
Casabonne et al,[22] 2007	39/80	23.08/21.25	1.10 (0.41-2.96)
Karagas et al,[21] 2006	252/461	9.92/6.07	1.70 (0.93-3.10)
Feltkamp et al,[11] 2003	160/333	5.00/2.10	2.20 (0.74-6.58)



The squares and horizontal lines correspond to the study-specific ORs and 95% CIs. The diamond represents the pooled OR and 95% CI of the overall population. The vertical dashed line indicates the overall pooled OR of 1.35. HPV indicates human papillomavirus; NA, not available; OR, odds ratio.

different HPV collection and detection methods, we performed a subgroup analysis restricted to studies that employed HPV serology. Third, we individually evaluated the association of each β-HPV type with cSCC. This type-specific meta-analysis constitutes another major quality of the evidence presented in this study.

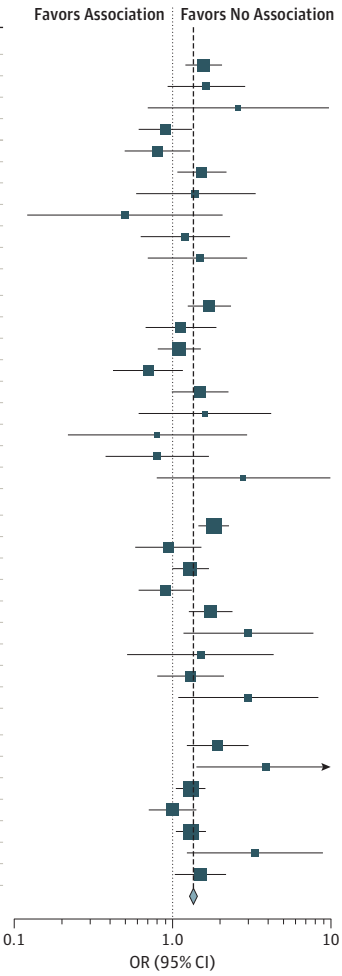
Study Limitations

One limitation of this study is the effect of UV light that might represent a confounder.[50] We attempted to minimize this effect by addressing it in our study quality assessment. Furthermore, most included studies were case-control studies that recruited from the same latitude level and adjusted for UV sunlight exposure.

Even though we have found a strong association between β-HPV and cSCC it is difficult to prove causality as our analysis is constituted mostly of case-control studies. However, the findings of 2 large prospective cohort studies[26,27] were in concordance with current evidence suggesting HPV involvement as a causal agent of the initiation process of cSCC. Moreover, our pooled analysis did not include every β-HPV type, a limitation that pertains to the

Figure 6. Forest Plot for the Subgroup Meta-analysis: Seroprevalence Only

Study, year	Cases/Controls, No.	Positive, %	RR (95% CI)
HPV-24 (I^2: 35%)			1.27 (1.03-1.57)
Bouwes Bavinck et al,[24] 2010	645/807	22.02/15.24	1.57 (1.20-2.05)
Iannacone et al,[29] 2012	173/300	20.81/12.33	1.63 (0.93-2.86)
Struijk et al,[28] 2006	41/48	19.51/8.33	2.60 (0.70-9.68)
Andersson et al,[27] 2012	633/NA	10.43/NA	0.90 (0.61-1.32)
Plasmeijer et al,[26] 2011	150/NA	14.67/NA	0.80 (0.50-1.29)
Karagas et al,[25] 2010	663/805	12.67/10.06	1.53 (1.07-2.18)
Waterboer et al,[23] 2008	43/77	37.21/27.27	1.40 (0.59-3.33)
Casabonne et al,[22] 2007	39/80	12.82/20.00	0.50 (0.12-2.06)
Karagas et al,[21] 2006	252/461	7.14/6.29	1.20 (0.63-2.30)
Feltkamp et al,[11] 2003	160/333	13.12/6.61	1.50 (0.76-2.95)
HPV-36 (I^2: 43%)			1.21 (0.95-1.54)
Bouwes Bavinck et al,[24] 2010	645/807	15.81/9.91	1.71 (1.25-2.34)
Iannacone et al,[29] 2012	173/300	23.12/17.33	1.13 (0.68-1.89)
Andersson et al,[27] 2012	633/NA	12.95/NA	1.10 (0.80-1.51)
Plasmeijer et al,[26] 2011	150/NA	10.67/NA	0.70 (0.42-1.16)
Karagas et al,[25] 2010	663/805	8.90/7.20	1.49 (0.99-2.25)
Waterboer et al,[23] 2008	43/77	32.56/24.68	1.60 (0.61-4.18)
Casabonne et al,[22] 2007	39/80	15.38/16.25	0.80 (0.22-2.94)
Karagas et al,[21] 2006	252/461	4.37/5.64	0.80 (0.38-1.70)
Masini et al,[20] 2003	46/84	19.57/8.33	2.80 (0.79-9.90)
HPV-38 (I^2: 58%)			1.44 (1.15-1.80)
Bouwes Bavinck et al,[24] 2010	645/807	37.67/24.91	1.82 (1.49-2.27)
Iannacone et al,[29] 2012	173/300	24.28/24.67	0.94 (0.58-1.52)
Andersson et al,[27] 2012	633/NA	20.54/NA	1.30 (1.00-1.69)
Plasmeijer et al,[26] 2011	150/NA	32.00/NA	0.90 (0.61-1.32)
Karagas et al,[25] 2010	663/805	18.70/12.05	1.74 (1.27-2.39)
Waterboer et al,[23] 2008	43/77	48.84/27.27	3.00 (1.17-7.70)
Casabonne et al,[22] 2007	39/80	25.64/17.50	1.50 (0.52-4.35)
Karagas et al,[21] 2006	252/461	13.49/10.85	1.30 (0.80-2.11)
Feltkamp et al,[11] 2003	160/333	5.62/2.70	3.00 (1.09-8.29)
HPV-genus β (I^2: 54%)			1.45 (1.17-1.79)
Iannacone et al,[29] 2012	173/300	73.41/60.33	1.93 (1.23-3.02)
Struijk et al,[28] 2006	54/52	37.04/13.46	3.90 (1.41-10.78)
Andersson et al,[27] 2012	NA/NA	NA/NA	1.30 (1.05-1.62)
Plasmeijer et al,[26] 2011	150/NA	70.67/NA	1.00 (0.71-1.41)
Karagas et al,[25] 2010	663/805	53.09/45.84	1.30 (1.04-1.62)
Waterboer et al,[23] 2008	NA/NA	NA/NA	3.30 (1.23-8.89)
Karagas et al,[21] 2006	252/461	32.54/24.73	1.50 (1.04-2.17)
Random-effects model using DerSimonian-Laird			1.35 (1.26-1.44)



The squares and horizontal lines correspond to the study-specific ORs and 95% CIs. The diamond represents the pooled OR and 95% CI of the overall population. The vertical dashed line indicates the overall pooled OR of 1.35. HPV indicates human papillomavirus; NA, not available; OR, odds ratio.

majority of studies assessing the topic. In addition, the method of HPV collection in our analysis was not PCR for HPV DNA from skin biopsy, the gold standard for detection. However, previous studies[7,34] demonstrated that eyebrow hair DNA and multiplex serology are reliable substitutes.

Research and Clinical Implications

The concordance between our epidemiological data in immunocompetent individuals and the molecular plausibility of type-specific involvement of β-HPV type 5, 8, 15, 17, 20, 24, and 38 in cSCC represents the evidence to strongly suggest a role for the HPV types in viral oncogenesis described herein. The associated increased risk of cSCC with these HPV types (30%-45%), the reported morbidity and mortality associated with cSCC and the increasing cost of care, constitute a burden on our health care system. This highlights the need to develop and test the efficacy of incorporating the above mentioned β-HPV subtypes into available HPV vaccines. Moreover, these efforts could render HPV vaccinations more widely accepted, possibly increasing the compliance rates for all HPV vaccines. A vaccine that includes these types of β-HPV will also be a major step toward precision medicine in the prevention of cSCC in solid organ transplant recipients, stem cell transplant recipients, and patients with melanoma undergoing *BRAF* inhibitor therapy.

Conclusions

This article represents, to our knowledge, the most extensive meta-analysis appraising the epidemiological association of β-HPV subtypes implicated in the pathogenesis of cSCC. This meta-analysis provides additional evidence of the involvement of β-HPV in the development of cSCC in immunocompetent individuals. Furthermore, this adds precision to the existing epidemiological findings by highlighting a significant, type-specific HPV association, which in turn is in concordance with the new arising molecular type-specific evidence.

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NOTABLE NOTES

Aloe Vera in Dermatology—The Plant of Immortality

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Aloe vera, or *Aloe barbadensis*, is perhaps the most ubiquitous plant in skin care products across the world and was used even in ancient Greece, Rome, Babylonia, and China. Historical evidence suggests that both the leaf and pulp of this plant have been used extensively to treat dermatological ailments and were believed to prevent skin senescence, acne, psoriasis, relieve pruritus, prevent premature graying of the hair, improve alopecia, and promote wound healing.[1] This Notable Note addresses the myriad of conditions aloe alleviates and provides a brief historical perspective of this "plant of immortality."

During the reign of Emperor Nero, around 50 BC, the Greek physician Dioscorides cited aloe as being able to alleviate skin irritation, sunburn, and acne. Subsequently, Pliny the Elder, a physician who lived from AD 23 to 79, confirmed in his encyclopedia, *Natural History*, the discoveries of Dioscorides.[2] While some studies show that aloe vera may inhibit growth of *Staphylococcus aureus*, *Shigella flexneri,* and other superficial mycoses-causing fungus, others suggest that it is ineffective in preventing *Propionibacterium acnes*–induced acne.[1]

In ancient Egypt, Cleopatra and Nefertiti incorporated aloe as part of their daily skin and beauty care. The dead were embalmed with aloe vera because of its antibacterial and antifungal properties. It was believed that in stopping the physical decomposition process, eternal life could be attained physically and also spiritually.

Aloe's antiaging and anti-inflammatory effects were well documented in the Papyrus Eber of 1550 BC. In Sanskrit, the plant is known as *Ghrita-Kumari*. *Kumar* means girl, and it was believed that this plant provided womanly youthfulness. Modern studies have shown that aloe gel significantly improves wrinkles and elasticity in photoaged human skin, increases collagen production in photoprotected skin, and decreases collagen-degrading *MMP-1* gene expression.[1]

Alexander the Great was thought to have used aloe juice to heal the war wounds on his warriors. Aloe was so important to Alexander that he arranged for transportable carts of planted aloe as supplies during his numerous battle campaigns. Aristotle even convinced the great conqueror to capture the island of Socotra specifically to gain possession of the precious aloe groves—allowing Alexander's army to acquire sufficient medication to heal the wounds of entire battalions.[3]

In modern times, mechanistic studies[1] have proven that aloe can enhance the synthesis of glycosaminoglycan components (hyaluronic acid and dermatan sulfate) in the matrix of a healing wound to increase the collagen content of the granulation tissue and the degree of crosslinking.

While many studies in modern times have validated the positive effects of aloe, contradictory observations exist for the treatment of psoriasis. As Pliny and Dioscorides described in ancient medical texts,[2] the true efficacy of aloe vera perhaps also depends on the interplay of its compounds, its geographic origin, and processing methods.

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