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Review Article

Human papillomavirus-associated skin cancers among organ transplant recipients: A systematic review and meta-analysis

Niloofar Faraji (MSc) [1]
Simin Farokhi (MD) [2]
Arshia Fakouri (MD) [2]
Shahab Aali (MD) [3]
Mahsa Motiei (MD) [4]
Kaveh Gharaei Nejad (MD) [5*]

1. Gastrointestinal and Liver Diseases Research Centre, Guilan University of Medical Sciences, Rasht, Iran
2. Razi Herbal Medicines Research Center, Lorestan University of Medical Sciences, Khorramabad, Iran
3. Department of Urology, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran
4. Pediatric Diseases Research Center, Guilan University of Medical Sciences, Rasht, Iran
5. Department of Dermatology, Skin Research Center, School of Medicine, Razi Hospital, Guilan University of Medical Sciences, Rasht, Iran

*** Correspondence:**
Kaveh Gharaei Nejad,
Department of Dermatology, Skin Research Center, Razi Hospital, Guilan University of Medical Sciences, Rasht, Iran

E-mail:
kavehgharaeinejad@gmail.com
Tel: +98 133550028

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Abstract

Background: Human Papillomavirus (HPV) is known to be associated with various types of skin neoplasms. Organ transplant recipients (OTR) are generally at a higher risk for developing skin neoplasms, including those related to HPV, due to their immunosuppressed state. In the current meta-analysis, we aimed to evaluate the frequency of HPV-related skin cancers and related factors among OTRs.

Methods: This meta-analysis study was conducted under the guidelines of the preferred reporting items for systematic review and meta-analysis (PRISMA). The generalized I^2 statistics was perfumed for assessing heterogeneity. Odds ratio (OR) and effective size were calculated in comprehensive meta-analysis (CMA) software Version 3. In addition, meta-regression analysis was conducted to examine the temporal trends in the incidence of HPV-related skin cancer among OTRs over the study years.

Results: Out of 417 potentially eligible studies, seven were included for final analysis. The most frequently reported skin cancers in OTRs were squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). The result of meta-analysis also revealed a high prevalence of 61.7% (95% CI: 35.4% - 82.5%) of HPV-related skin cancer among OTRs. The male-to-female ratio was 2.14 (95% CI 0.58-7.87), and the mean time from transplantation to the first diagnosis of skin cancer was about eight years. The frequency of HPV among tumor lesions ranged from 37.7% to 74.1%.

Conclusions: These findings collectively provide insights into the prevalence of HPV among OTRs with skin neoplasms, emphasizing the need for careful consideration of heterogeneity when interpreting the overall estimate.

Keywords: Human papillomavirus, Transplant, Organ transplantation, Neoplasm.

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Organ transplant recipients (OTRs) are at high risk for developing various malignancies due to long-term immunosuppressive therapy (1). Among the numerous factors contributing to cancer development in this population, human papillomavirus (HPV) infection has emerged as a significant risk factor for certain skin cancers (2, 3). The prevalence of HPV-associated skin cancers, including squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), among OTRs is notably higher compared to the general population (4). In addition to the increased prevalence of HPV-associated cancers among OTRs, the clinical course of these cancers in this population tends to be more aggressive and challenging to manage (5). Furthermore, due to the compromised immune system, HPV-related skin cancers in OTRs often exhibit rapid growth, increased recurrence rates, and a higher potential for metastasis than in non-immunosuppressed individuals (6). OTRs are more susceptible to non-melanoma skin cancers about 15 years younger than immunocompetent individuals (7). These factors significantly contribute to a less favorable prognosis and increased mortality rates associated with HPV-related skin cancers within this vulnerable population. Immunosuppressive medications administered to prevent organ rejection significantly impact the immune system's ability to control infections (8).

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Consequently, OTRs experience a higher likelihood of persistent HPV infection and subsequent development of skin cancers (9). The oncogenic potential of HPV in the context of organ transplantation has been linked to various HPV genotypes (10), such as high-risk types (HPV-16 and HPV-18) that have been implicated in the development of SCC (11). In addition, beta-HPVs, such as HPV-5 and HPV-8, have long been associated with keratinocyte carcinoma in immunosuppressed individuals (12, 13). The carcinogenesis of beta-HPV is associated with sunlight exposure (14). Implementing effective preventive measures is crucial, considering the heightened risk of HPV-associated skin cancers in OTRs (15). Vaccination against high-risk HPV types has shown promise in reducing the incidence of HPV infection and related cancers in the general population (16, 17). However, the optimal use and efficacy of HPV vaccines in organ transplant recipients, particularly those already immunosuppressed, warrant further investigation (18, 19). A multidisciplinary approach involving dermatologists, oncologists, and transplant specialists is crucial to address the elevated risk and unique challenges posed by HPV-related skin cancers in OTRs. Regular dermatological screening and surveillance are essential to detect precancerous and cancerous lesions early when treatment outcomes are more favorable. Additionally, topical therapies, surgical interventions, and photodynamic therapy may be employed to manage and treat HPV-associated skin cancers in OTRs (20, 21). The prevalence of HPV-associated skin cancers is notably higher in OTRs due to the immunosuppressive effects of long-term therapy. Therefore, understanding the specific HPV genotypes associated with skin cancer development is crucial for targeted interventions and personalized management (22, 23). In addition, education and awareness campaigns targeting healthcare professionals and OTRs are necessary to emphasize the importance of sun protection, self-examination, and early reporting of suspicious skin lesions to reduce the burden of HPV-associated skin cancers among OTRs and improve their long-term outcomes. Therefore, we aimed to explore the prevalence of HPV-associated skin cancers in OTRs.

Methods

Settings: This systematic review and meta-analysis study was conducted to identify the frequency of HPV-related skin cancers among OTRs according to the Systematic Review and Meta-analysis (PRISMA) guideline (24).

Search strategy: We searched four international databases, including PubMed, Embase, Web of Science, and Google Scholar from inception up to Jun 2023, using the following keywords: "HPV", "Human papillomavirus", "Skin cancer", "Skin malignancies", "Skin neoplasm", "Cutaneous cancer", "Cutaneous malignancies", "Squamous cell carcinoma", "Basal cell carcinoma", "Melanoma", "Non-melanoma", "Organ recipient", "Organ transplant", "Transplant recipient", "Organ transplant recipient".

Eligibility criteria and data extraction: All studies that investigated the identification of various types of HPV and associated skin cancers among OTRs of any age and gender were considered for inclusion in this study. Inclusion criteria required that the diagnosis of HPV and skin cancers be based on clinical and/or histologic criteria, and the full text of the study must be accessible, containing at least one of the following data points: use of any immunosuppressive drugs, assessment for HPV, gender distribution, onset timing of skin cancers, duration of transplantation until the onset of skin cancer, type of therapeutic intervention for skin cancer, and availability of the complete text. The selection process involved meticulous examination by three independent researchers, with any discrepancies or disagreements resolved through face-to-face consultations. The quality assessment of included studies was performed using the Joanna Briggs Institute (JBI) critical appraisal checklists (25, 26) (supplementary 1).

Statistical analysis: All data were analyzed using comprehensive meta-analysis (CMA) statistical software Version 3. Data were pooled when three or more studies were available for a distinct outcome. The I^2 statistics (the significant level was considered 50%<) were obtained to determine the heterogeneity of the results and studies with I^2>50% were considered heterogenic. A random-effects model was used to assess the prevalence of heterogeneity; otherwise, the fixed-effect model was applied. The odds ratio (OR) and effective size were calculated based on a 95% confidence interval (CI). To investigate the source of heterogeneity, a sensitivity analysis was performed. Moreover, biases of study results were evaluated and reported by Egger's regression, and meta-regression analysis was applied to estimate the trend of the year of studies.

Results

Study selection process: The search results encompassed a comprehensive examination of international databases and yielded 417 potentially relevant studies. Following the meticulous removal upon a careful assessment of studies, the pool was streamlined to seven eligible studies that were

suitable candidates for qualitative and quantitative analyses (figure 1).

Characteristics of included studies: The primary data were extracted and reported in Table 1. According to this table, the most frequently reported skin cancer was SCC and BCC among OTRs. Among the total number of tumoral lesions from a skin biopsy, HPVs were detected in 40 lesions out of 44 warts, 41 out of 74 SCC, 12 out of 19 Bowen's disease, 3 out of 38 BCC, and 10 out of 19 keratoacanthoma. Moreover, the total frequency of males was higher than females among OTRs with HPV-related skin cancers. Furthermore, the renal graft was the most frequently transplanted organ among patients.

Main result: This meta-analysis focused on assessing the pooled prevalence of HPV among organ recipients diagnosed with skin cancer (table 2). From six studies and 122 patients, the pooled prevalence was estimated at 0.617 (95% CI: 0.354 - 0.825), indicating that approximately 61.7% (35.4% - 82.5%) of organ recipients with skin cancer were found to be positive for HPV.

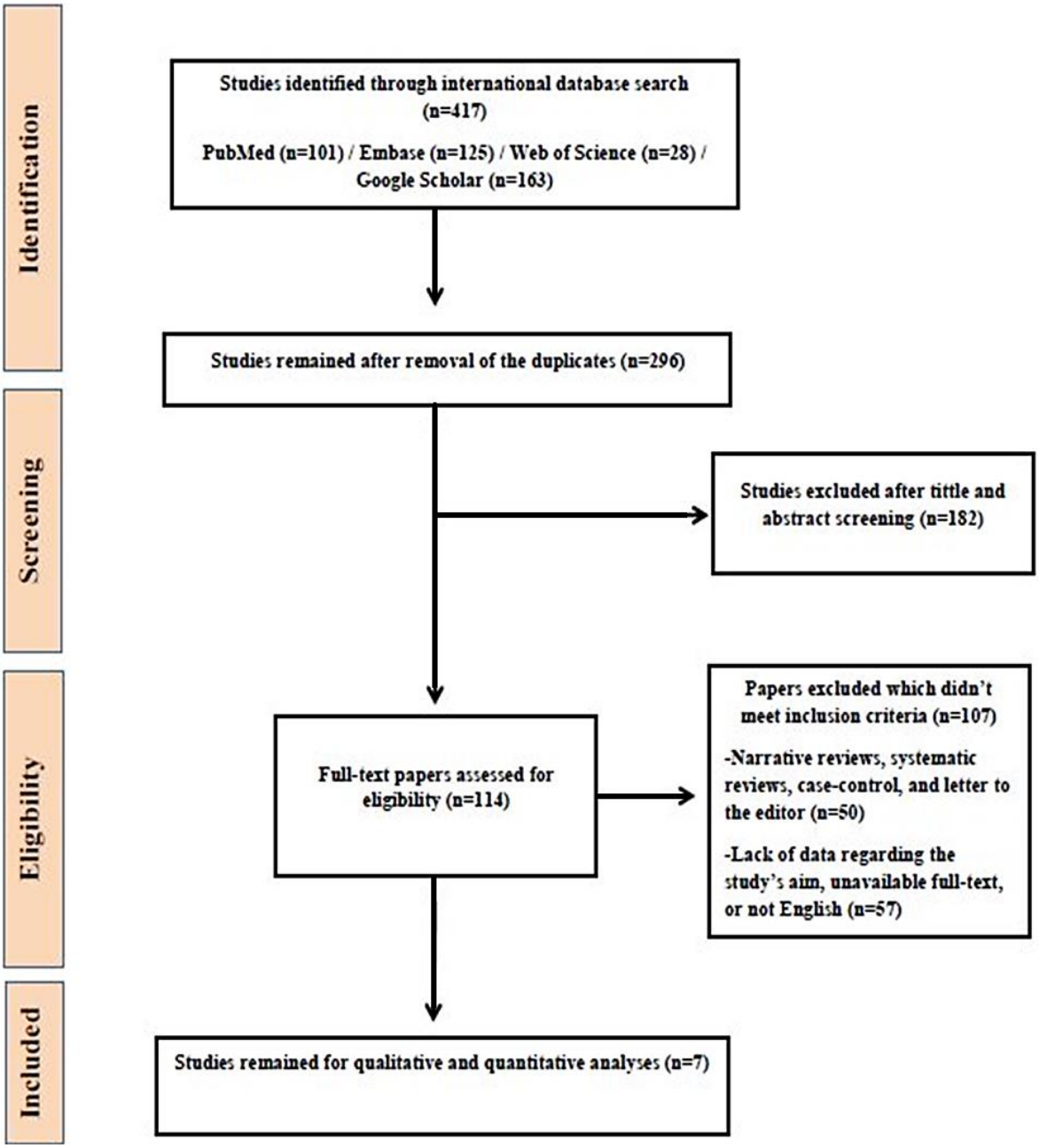

Figure 1. The study selection flowchart

Table 1. Total data of included studies on HPV-related skin cancers among organ transplant recipients

First author, year	Duration of studies	HPV/ OTRs with skin cancers	HPV/ Tumoral lesions	Females/males with HPV-related skin cancers	Organ	Mean time±SD of onset of skin cancer from transplantation (year)	OTRs with SCC / BCC / BD/ KA	Reference
Rudlinger, 1986	1986	2/6	3/9	1/1	Renal graft	-	3/0/0/0	(27)
Euvrard, 1993	1990-1993	11/20	25/52	1/10	Renal graft	9.8±3.8	8/2/1/6	(28)
De Villiers, 1997	1982-1994	-	38/33	-	Renal graft	-	9/0/0/0	(29)
Dang, 2006	2006	5/6	7/9	3/2	Renal graft & heart	-	6/1/1/0	(30)
Borgogna, 2014	1998-2009	4/15	17/53	0/4	Renal graft	7±0.5	14/31/1/7	(31)
Genders, 2015	1990-2006	60/60	-	20/40	Renal graft & pancreas	8.2±0.5	14/24/0/0	(12)
Pritchett, 2016	2011-2016	9/15	12/19	2/6	Pancreas & kidney & heart	7.8	1/4/13/0	(32)

OTR: Organ transplant recipient, SCC: Squamous cell carcinoma, BCC: Basal cell carcinoma, BD: Bowen's disease, KA: Keratoacanthoma

Table 2. The result of heterogeneity and biases among included studies on HPV-related skin cancers among organ transplant recipients

Variables	Number of studies	95% CI			Heterogeneity			Egger's regression intercept	
		Odds ratio/Point estimate	Lower	Upper	*Q* value	I^2 (%)	*P*-value	*P*-value	t-value
Prevalence of HPV-related skin cancer	6	0.617	0.354	0.825	17.630	71.639	0.003	0.223	4.437
Gender frequency	5	2.144	0.584	0.768	2.917	0.000	0.250	0.017	4.768
The mean time of the first diagnosis of skin cancer from transplantation to the first	4	8.074	7.695	8.453	273.427	98.903	<0.001	0.481	0.857
Prevalence of HPV among all skin tumor lesions	6	0.568	0.377	0.741	23.846	79.032	<0.001	0.304	1.177

Borgogna et al. (31) and Rudlinger et al. (27) reported a lower frequency of HPV-related skin cancer among OTRs, respectively, while Genders et al. (12) and Dang et al. (30) demonstrated the most higher frequency, respectively, among the publications; meanwhile, the reported prevalence of Pritchett et al. (32) and Euvrard et al. (28) were close to overall pooled prevalence, respectively (figure 2A). Potential publication bias was checked by running Egger's regression intercept, and no significant bias in the meta-analysis was reported (t-value=4.437, *P*=0.259) (figure 2B). The results of a sensitivity analysis illustrated no significant differences by omitting each study on the overall pooled prevalence (figure 2C). Moreover, subgroup analysis by different types of HPV among reported skin

cancers demonstrated a higher frequency of coexistence of four types of HPV (Alpha, Beta, Gamma, and Mu) in evaluated tumoral lesions compared to the exitance one type or two (figure 2D). According to the results of the meta-regression analysis on seven studies and 818 OTRs, there was a non-significant association between the year of study and the prevalence of HPV-related skin cancer (coefficient=-0.0385, *P*=0.3445). Therefore, based on the available data, no evidence suggests a significant decreasing trend in the prevalence of HPV-related skin cancer over the years (figure 3). The meta-analysis found a consistent effect size of male/female ratio in six studies, about 2.14 (95% CI 0.58-7.87) for gender frequency among OTRs with HPV-related skin cancer, with no significant heterogeneity (Q-value=2.917, *P*=0.5718, I^2=0%), (figure 4A). The funnel plot analysis indicated potential publication bias for gender frequency, as evidenced by Egger's regression (t-value=2.204, *P*=0.017). These findings suggest an underrepresentation of smaller studies with negative or non-significant results (figure 4B). The forest plot analysis of the mean time from transplantation to the first skin cancer diagnosis among 745 OTRs in four studies revealed a random effects model with a point estimate of 8.074 (95% CI, 7.695-8.453) (figure 4C).

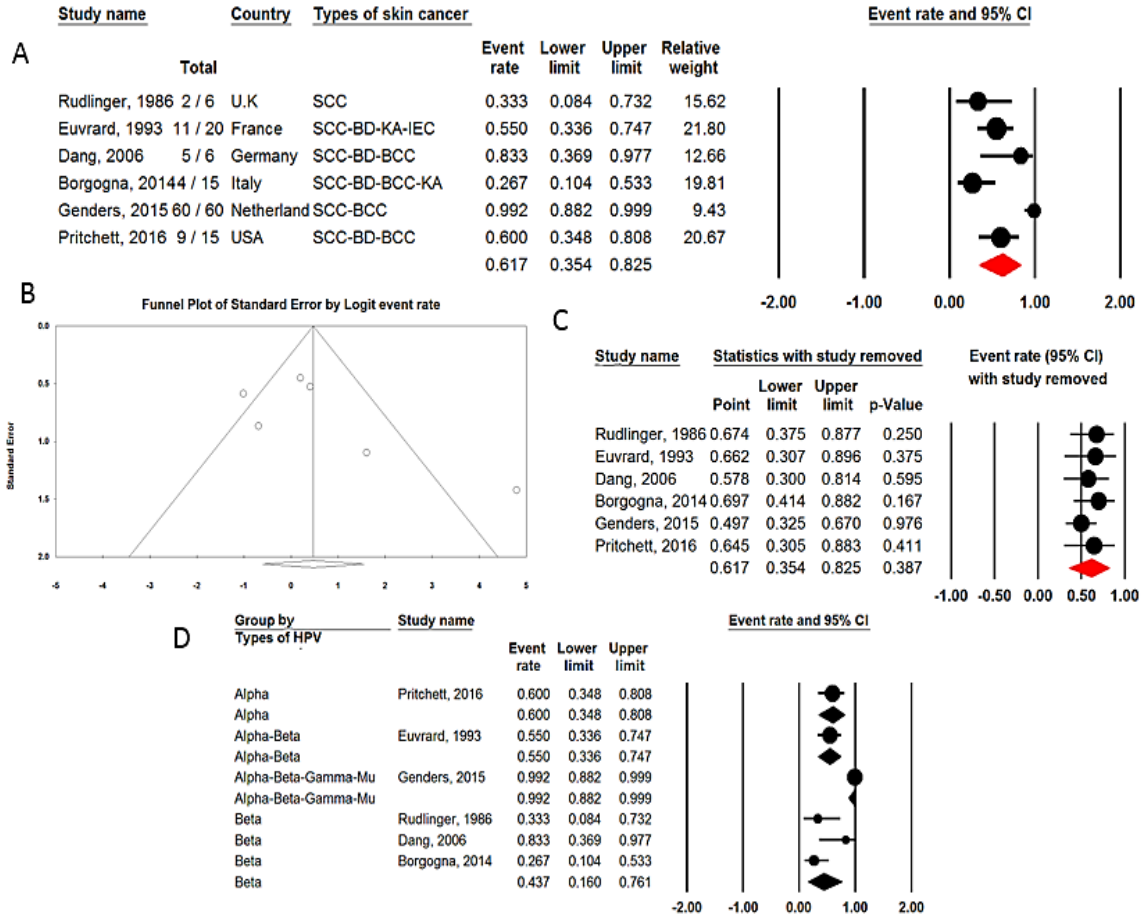

Figure 2. A) Forest plot of the Frequency of HPV-related skin cancers among organ transplantation recipients. [SCC: Squamous cell carcinoma; BCC: Basal cell carcinoma; BD: Bowen's disease; KA: Keratoacanthoma. The random-effects model was applied to analyze the relationship between HPV-related skin cancers and organ transplant recipients. The point estimate for the effect size was found to be 0.617 (95% CI: 0.354 - 0.825), suggesting a positive association. The z-value for the test of the null hypothesis was 0.865 (P= 0.387), which was not statistically significant. The random-effects (I^2>50%) estimate indicated a potential variability among the studies.]. **B)** Funnel plot for visual evaluation of biases of studies' results on HPV-relates skin cancers among organ transplantation recipients. [*Egger's regression intercept:* Intercept=2.804; Standard error=1.950; 95% lower limit=-2.611; 95% upper limit=8.221; t-value=1.437; df= 4; P=0.223. *Begg and Mazumdar rank correlation:* Kendall's Tau with continuity correction: Tau=0.400; z-value for tau=1.124; P=0.259]. **C)** Sensitive analysis to illustrate the effect of omitting each study on the overall pooled stimulated point on the frequency of HPV-related skin cancers among organ transplantation recipients. **D)** Forest plot of the frequency of HPV-relates skin cancers, subgroups by types of HPV among organ transplantation recipients.

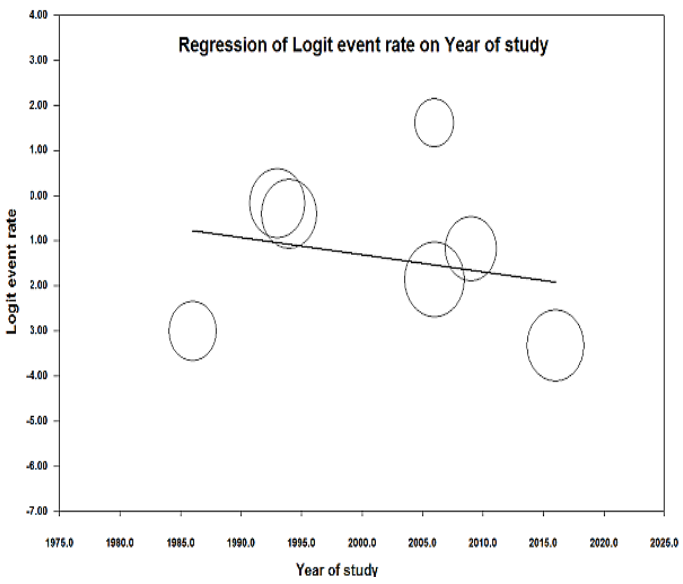

Figure 3. The scattered plot of meta-regression for trends of HPV-relates skin cancers among organ transplantation recipients in different years. [The meta-regression analysis using Model 1 with random effects (MM), Z-Distribution, and Logit event rate revealed that the intercept coefficient was not statistically significant (coefficient = 75.6326, P= 0.3531). The covariate "year of study" also showed no significant relationship with the outcome (coefficient = -0.0385, P= 0.3445). The model did not have collectively significant coefficients (Q = 0.89, df = 1, P= 0.3445). The goodness of fit test indicated significant variability across studies (Tau^2 = 0.8417, Tau = 0.9174, I^2 = 85.48%, Q = 34.44, df = 5, p< 0.001). Model 1 significantly reduced the between-study variance compared to the null model (Tau^2 = 1.3190, Tau = 1.1485, I^2 = 90.21%, Q = 61.28, df = 6, P< 0.001), explaining 36% of the total between-study variance (R^2 analog = 0.36)].

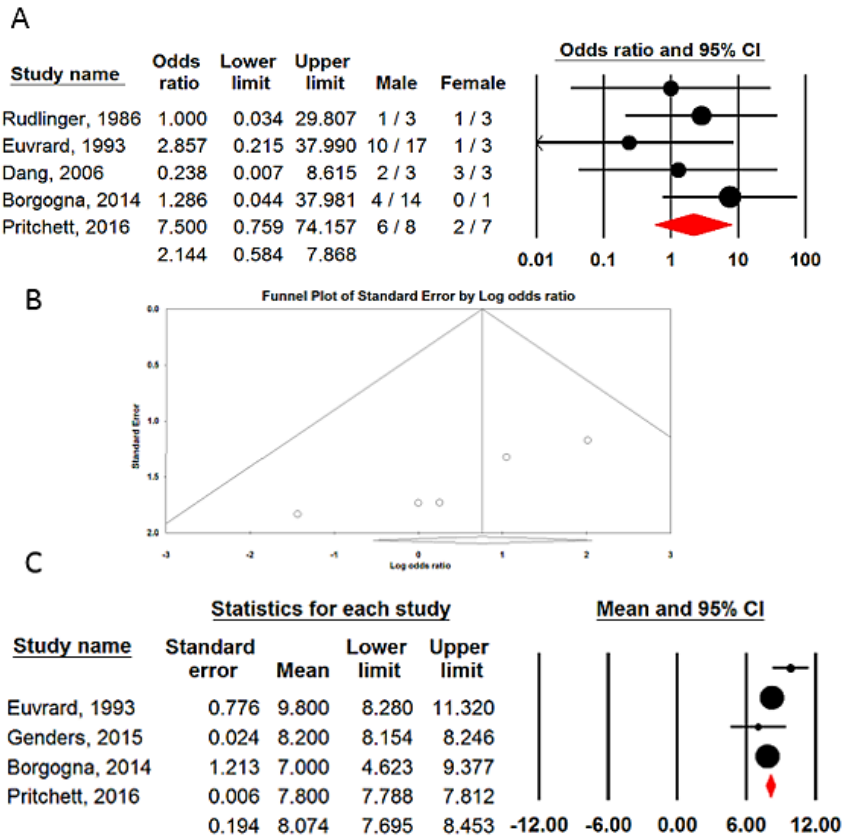

Figure 4. A. Forest plot of gender frequency of HPV-relates skin cancers among organ transplantation recipients with skin cancers. [Using both fixed and random effects models, the meta-analysis reported similar effect sizes for the gender frequency among OTRs with HPV-related skin cancer. The fixed and random effects models produced a point estimate 2.14 (95% CI, 0.58-7.87). The heterogeneity analysis showed a Q-value of 2.917 with df=4 and P=0.5718, indicating no significant heterogeneity among the studies. Additionally, the I^2=0% suggests that all the variability observed in the meta-analysis can be attributed to random chance.] B. Funnel plot of visual evaluation of biases of studies' results on the gender frequency of HPV-relates skin cancers among organ transplantation recipients with skin cancers. [*Egger's regression intercept:* Intercept=-3.978; Standard error=0.834; 95% lower limit=-6.632; 95% upper limit=-1.323; t-value=4.768; df=3; P=0.017. *Begg and Mazumdar rank correlation:* Kendall's Tau with continuity correction: Tau=-0.900; z-value for tau=2.204; P=0.027]. C. Forest plot of the mean time from transplantation to the first skin cancer diagnosis among organ transplantation recipients. [The random-effects model was 0.8.074 (95% CI: 7.695 – 8.453). The random-effects (I^2>50%, df=3, Q-value=273.427) estimate indicated a potential variability among the studies (p<0.001)].

The forest plot analysis of the frequency of HPV among 175 evaluated tumoral lesions in six studies from skin biopsy in the random effects model revealed 56.8% frequency (Event rate=0.568, 95% CI, 0.377-0.741), with the highest frequency reported in De Villiers et al. and Dang et al.' studies, respectively (29, 30), while Rudlinger et al. and Borgogna et al. reported less frequencies in their studies (27, 31), (figure 5A). The following funnel plot for bias analysis indicates no significant biases of publications (t-value=1.177, *P*=0.304) (figure 5B).

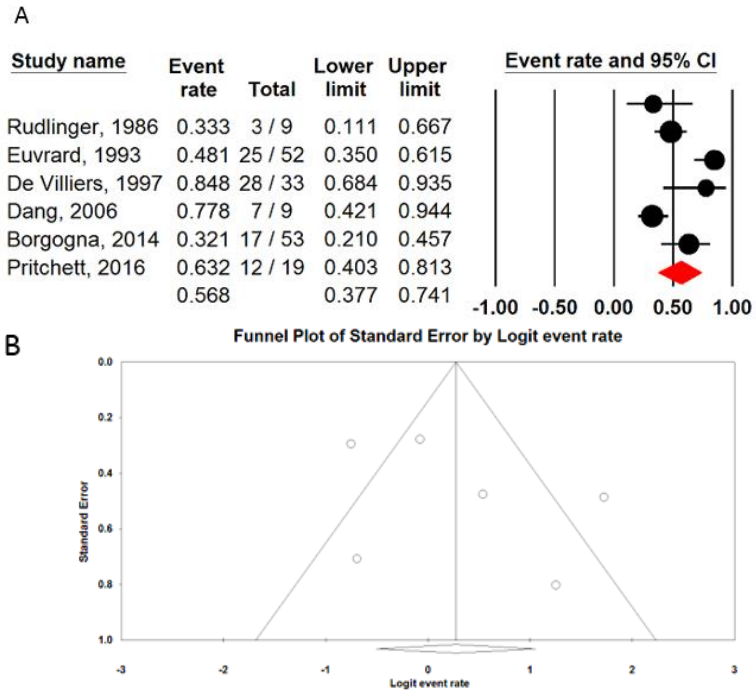

Figure 5. A. Forest plot of the frequency of HPV detection in skin tumor lesions among organ transplantation recipients with skin cancers. [The random-effects model was 0.568 (95% CI: 0.377 – 0.741). The random-effects (I^2>50%, df=5, Q-value=23.846) estimate indicated a potential variability among the studies (p<0.001*)*]. B. Funnel plot of visual evaluation of biases of studies' results on the frequency of HPV detection in skin tumor lesions among organ transplantation recipients. [*Egger's regression intercept*: Intercept=2.772; Standard error=2.353; 95% lower limit=-3.763; 95% upper limit=9.307; t-value=1.177; df=4; P=0.304. *Begg and Mazumdar rank correlation:* Kendall's Tau with continuity correction: Tau=-0.266; z-value for tau=0.751; P=0.452].

Discussion

The present meta-analysis yielded seven eligible studies, providing valuable insights into the frequency of skin cancers, HPV prevalence, gender distribution, and time from transplantation to the occurrence of skin cancer in OTRs. Immunosuppressed solid OTRs have a heightened risk of developing cutaneous carcinomas with a higher incidence than the general population (33-35). In the current study, the pooled prevalence of HPV among OTRs with skin cancer was about 61.7%, which was more prevalent in males. In terms of gender distribution, a higher frequency of HPV-related skin cancer among males compared to females was reported in different studies (36–38). A study by Reuschenbach et al. showed that the highest prevalence of high-risk HPV was found in SCC lesions (46.2%) in immunosuppressed patients and 23.5% in immunocompetent ones (39). Another study reported 73.3% of HPV DNA detection in immunosuppressed patients and 53.3% in immunocompetent patients with non-melanoma skin cancer (40). This discrepancy may be attributed to differences in the study populations, sample sizes, or methods of HPV detection and typing. Our analysis revealed that SCC and BCC were the most frequently reported types of skin cancer among OTRs. Studies noted that non-melanoma skin cancers were the two most prevalent skin cancer types among OTRs (15, 41, 42).

Additionally, the current study demonstrated different prevalence of HPV in various tumor lesions, with HPV detection rates of 90.9% in warts, 55.4% in SCC, 63.2% in Bowen's disease, 7.9% in BCC, and 52.6% in Keratoacanthoma. These findings highlight the significant association between HPV and skin cancer development in OTRs. A cohort study reported the prevalence of 28.6% of non-melanoma skin cancers among 518 kidney transplant

recipients (43). The development of non-melanoma skin cancers among OTRs has been reported to be strongly influenced by the presence of HPV, specifically beta-HPV (4, 44-46). Nindle et al. reported that OTRs have a higher prevalence rate of HPV in cutaneous SCC, ranging from up to 90%, compared to the prevalence rate in normal skin, which ranges from 11% to 32% (47). The results of a meta-analysis on the burden of anal SCC, squamous intraepithelial lesions, and HPV16 infection in solid OTRs reported the pooled prevalence of six studies by the incidence of anal SCC in solid OTRs compared to the general population, with a standardized incidence ratio of 6.8 (95% CI, 4.3-10.9). The absolute incidence rate was reported to be 12.3 (95% CI, 10.4-14.7) per 100,000 person-years, based on five studies with a total of 1,079,489 person-years of follow-up (48).

Our study showed a higher frequency of multiple HPV types in tumor lesions compared to the presence of single or two types, indicating the potential role of multiple HPV infections in the development of skin cancer in OTRs, and the beta-HPV was the most frequently detected type. OTRs with five or more different beta-HPV types detected in their eyebrow hair had a 1.7 times higher risk of developing SCC than OTRs with 0 to 4 different types. The hazard ratio for this risk was 1.7 (95% CI 1.1-2.6). Similarly, OTRs with high beta-HPV loads also had a similar increased risk of SCC, with a hazard ratio of 1.8 (95% CI 1.2-2.8) (4). Chahoud et al., in their meta-analysis study, illustrated that the overall association between beta-HPV and SCC was significant in immunocompetent individuals with an adjusted pooled OR of 1.42 (95% CI: 1.18-1.72). Their subgroup analysis highlighted the significant association between overall beta-HPV and HPV subtypes with SCC (49). Genders et al. observed that among 445 OTRs, beta-HPV seropositivity at transplantation was associated with a 2.9-fold higher risk of developing SCC, BCC, and keratinocyte carcinomas, providing evidence of beta-HPV role in skin carcinogenesis (12).

Moreover, the average time from transplantation to the first diagnosis of skin cancer among OTRs in the current study was about eight years, illustrating that skin cancer tends to manifest relatively early after transplantation in this population. Kotaro et al. reported that the average time interval until cancer diagnosis was 3.7 years. They also highlighted the importance of race and UV on the susceptibility of kidney transplant recipients to skin cancer. They reported that out of 447 kidney transplant recipients (130 Caucasians and 317 African Americans), 31 (6.9%) recipients developed post-transplant skin cancer (24 Caucasians and 11 African Americans), and the average time interval until cancer diagnosis was 3.7 years (50). In light of these comparisons, our meta-analysis adds insight to the existing body of evidence, reaffirming the integral role of HPV in developing skin cancer among OTRs. The concordance between our findings and those of other studies underscores the reliability and generalizability of our results. However, while this study contributes to a deeper understanding of HPV-related skin cancer in OTRs, further research is warranted to elucidate the precise mechanisms by which HPV infection contributes to skin carcinogenesis in this immunocompromised population. While the study contributes valuable insights, it is not free from limitations. First, there may be heterogeneity among the studies in terms of study design, sample sizes, and methods of HPV detection, which could introduce variability in the results. Furthermore, the generalizability of the findings may be limited to the specific population of OTRs included in the analyzed studies. These limitations should be considered when interpreting the results, and future research should address these concerns further to enhance the understanding of HPV-related skin cancer in OTRs. In summary, this meta-analysis and the supporting studies demonstrate a considerable prevalence of HPV-related skin cancer among OTRs and provide valuable insights into the prevalence, characteristics, and factors associated with HPV-related skin cancer among OTRs. The findings highlight the significant burden of HPV-related skin cancer in this population and emphasize the need for continued monitoring, prevention strategies, and appropriate management. These results underscore the importance of addressing HPV-related skin cancer as a critical concern in OTRs to improve patient outcomes.

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Not applicable.

Ethics approval: Ethical approval was not required for this study.

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Conflict of interests: The authors declare no conflict of interest.

Authors' contribution: Conceptualization: NF and KGH; Search strategy: NF, SF and AF; Data extraction: NF, SF, and AF; Quality assessment: MM, SF, and AF; Formal analysis: NF, MM, and SHA; Writing original draft: NF, SHA, MM, and KGH. Supervision: KGH. Revising and writing he final manuscript: NF, SHA, KGH.

Data availability: The datasets used are available from the corresponding author upon reasonable request.

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