ORIGINAL ARTICLE

Voriconazole exposure and risk of cutaneous squamous cell carcinoma among lung or hematopoietic cell transplant patients: A systematic review and meta-analysis

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Background: Current evidence about the association between voriconazole and risk of cutaneous squamous cell carcinoma (SCC) remains inconsistent.

Objective: To assess the association between voriconazole use and risk of SCC.

Methods: We systematically searched PubMed and Embase and performed a random effects model meta-analysis to calculate the pooled relative risk (RR) with a 95% confidence interval (CI).

Results: Of the 8 studies involving a total of 3710 individuals with a lung transplant or hematopoietic cell transplant that were included in the qualitative analysis, 5 were included in the meta-analysis. Use of voriconazole was significantly associated with increased risk of SCC (RR, 1.86; 95% CI, 1.36-2.55). The increased risk did not differ according to type of transplantation or adjustment for sun exposure. Longer duration of voriconazole use was found to be positively associated with risk of SCC (RR, 1.72; 95% CI, 1.09-2.72). Voriconazole use was not associated with increased risk of basal cell carcinoma (RR, 0.84; 95% CI, 0.41-1.71).

Limitations: There were some heterogeneities in the retrospective observational studies.

Conclusions: Our findings support an increased risk of SCC associated with voriconazole in individuals with a lung transplant or hematopoietic cell transplant. Routine dermatologic surveillance should be performed, especially among individuals at high risk of developing SCC. (J Am Acad Dermatol https://doi.org/10.1016/j.jaad.2018.08.010.)

Key words: meta-analysis; squamous cell carcinoma; transplantation; voriconazole.

Nonmelanoma skin cancer (NMSC) is the most common malignancy among individuals who have undergone solid organ transplantation[1] or received a hematopoietic cell transplant (HCT).[2,3] The most common NMSC among this population is cutaneous squamous cell carcinoma (SCC), followed by basal cell carcinoma (BCC),[1] which together account for 95% of skin cancers in organ transplant recipients.[4] Individuals after solid organ transplantation had a higher risk for NMSC compared with the general population,[5,6] and this risk increased with time after transplantation.[7] Moreover, NMSC appears to be more aggressive among solid organ transplant recipients than in the general population, which increases mortality among solid organ recipients.[8,9] Several risk factors,

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including history of frequent sun exposure, male sex, Fitzpatrick skin type I to III, older age at transplantation, immunotherapies, and underlying disease were found to be associated with increased risk of NMSC after transplantation.[10-14]

Since 2002, voriconazole has been used to manage or prevent fungal infections, which are important complications after a lung transplant (LT) or HCT and can result in significant morbidity and mortality.[15,16] However, voriconazole can cause significant toxicity and side effects, including hepatotoxicity, visual disturbances, and photosensitivity.[17] Recently, the increased risk of NMSC (primarily SCC) associated with voriconazole use attracted our attention. Voriconazole and its major hepatic metabolite, voriconazole N-oxide (VNO) may generate reactive oxygen species and induce DNA damage by sensitizing keratinocytes to ultraviolet (UV) A light.[18] However, current evidence regarding the association between use of voriconazole and risk of SCC among the patients with an LT or HCT remains controversial.[7,19-26] The conflicting results might be due to the small sample size in individual studies, heterogeneity in populations, duration of use or dose of voriconazole, or the use of combination treatments. We therefore conducted this systematic review and meta-analysis of available observational studies to critically analyze and synthesize the evidence regarding the association between use of voriconazole and risk of SCC or BCC following a LT or HCT.

CAPSULE SUMMARY

- Voriconazole exposure and longer duration of voriconazole use were found to be significantly associated with increased risk of squamous cell carcinoma.
- Regular dermatologic surveillance should be considered for the patients taking voriconazole, especially those at high risk of developing squamous cell carcinoma.

MATERIALS AND METHODS

The study was performed in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines for reviews of observational studies.[27]

Search strategy and study selection

PubMed and Embase were searched from inception to September 2017 to identify eligible observational studies (Supplemental Table I; available at http://www.jaad.org). Additionally, we searched the reference lists of relevant reviews and included studies. Two reviewers (H.T. and W.S.) selected those studies that met the following criteria: (1) were observational (both prospective and retrospective) studies; (2) evaluated the association between voriconazole and risk of SCC or BCC; and (3) reported the outcome of SCC or BCC. In the event of multiple reports using the same database, we included the latest study only. Conference abstracts were excluded because they offered limited information on study quality, population, and outcomes.

Data extraction and quality assessment

We collected information on study design, data source, number of participants, age, selection criteria, exposure definition, adjusted covariates, and outcomes of interest. Estimates on risk of SCC or BCC were extracted if appropriate. The quality of the observational study was assessed by using a 9-star scoring system as described by the Newcastle-Ottawa quality assessment scale, with totals of 7 to 9 and 5 to 6 stars indicating high and moderate quality, respectively.[28] Two reviewers (H.T. and W.S.) independently extracted the data and assessed the quality of each study. We contacted the original author for more information if any information was missing. Any disagreement was resolved by consensus or referral to a third reviewer (J.H.).

Statistical analysis

To account for heterogeneity between studies, a random effects model was used to calculate the pooled relative risk (RR) and 95% confidence interval (CI) for the association between voriconazole exposure and risk of SCC or BCC. Statistical heterogeneity was quantified by using the I^2 statistic (low heterogeneity, 25%; moderate heterogeneity, 50%; and high heterogeneity, 75%).[29] Subgroup analysis by type of transplantation or adjustment for sun and/or UV exposure was performed to assess the consistency of the association between voriconazole and SCC risk. A sensitivity analysis was performed by removing 1 study at a time from the pooled analysis to evaluate its influence on the pooled estimate. The development of the evidence on the association between voriconazole and risk of SCC was tested by using a cumulative meta-analysis based on the date of publication. A visual inspection of the funnel plots and the Begg and Egger tests were applied to examine potential publication bias. All statistical analyses were performed with STATA software (version 14, Stata Corp, College Station, TX).

Abbreviations used:

BCC: basal cell carcinoma
CI: confidence interval
HCT: hematopoietic cell transplant
LT: lung transplant
NMSC: nonmelanoma skin cancer
RR: relative risk
SCC: squamous cell carcinoma
UV: ultraviolet
VNO: voriconazole N-oxide

RESULTS

Study selection and study characteristics

Of 151 citations retrieved from electronic databases, 8 observational studies involving a total of 3710 individuals met the eligibility criteria and were included in our systematic review (Fig 1). Two studies used the same database[21,22]; thus we included the latest study only.[22] Of the 8 studies included, 7 were retrospective cohort studies and 1 was a retrospective case-control study. The characteristics and main results of the included studies are presented in Table I and Supplemental Table II (available at http://www.jaad.org), respectively. In all, 4 studies were assessed as being of high quality,[20,22,24,25] whereas the remaining 4 studies were determined to be of moderate quality (Supplemental Table III; available at http://www.jaad.org).[7,19,23,26] In all, 6 studies providing adequate data on the risk of SCC or BCC associated with voriconazole were included in the meta-analysis.

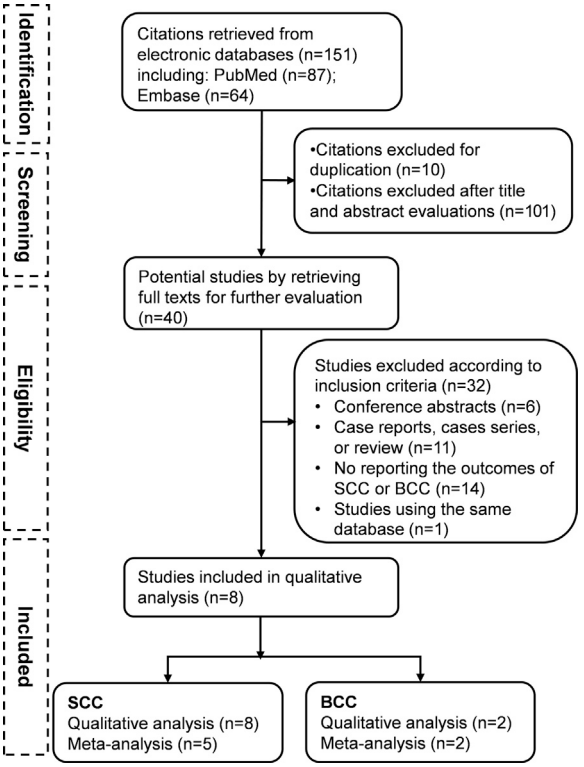

Fig 1. Flowchart of the identification of eligible studies. *BCC,* Basal cell carcinoma; *SCC,* squamous cell carcinoma.

SCC risk

The 8 studies, which involved a total of 3710 patients, assessed the relationship between voriconazole exposure and risk of SCC.[7,19,20,22-26] Of the 8 studies, 6 were performed in individuals with an LT[7,20,22,24-26] and 2 were performed in individuals with an HCT.[19,23] A total of 405 SCC cases were identified among these patients (crude incidence, 10.9%); however, only 5 studies (3122 patients with 272 SCC cases) provided relevant data on risk of SCC and were included in the meta-analysis.[7,19,22,23,25] The overall RR for SCC risk associated with voriconazole was 1.86 (95% CI, 1.36-2.55), with low heterogeneity across studies (I^2 = 4.5%) (Fig 2). Subgroup analysis by transplantation type showed a higher risk of SCC associated with voriconazole in both LT recipients (RR, 1.65; 95% CI, 1.02-2.68) and HCT recipients (RR, 2.29; 95% CI, 1.37-3.82) (Supplemental Fig 1; available at http://www.jaad.org). Significantly increased risk of SCC was associated with voriconazole, regardless of whether a study was adjusted for sun and/or UV exposure (adjusted RR, 2.42; 95% CI, 1.38-4.22; unadjusted RR, 1.64; 95% CI, 1.04-2.58) (Supplemental Fig 2; available at http://www.jaad.org).

The significant association between voriconazole and increased risk of SCC remained robust in the sensitivity analysis when each study was removed from meta-analysis 1 study at a time (Supplemental Fig 3; available at http://www.jaad.org). Our cumulative meta-analysis ordered by publication year indicated that the association became significant beginning in 2017 (Supplemental Fig 4; available at http://www.jaad.org). There was no evidence of substantial publication bias according to the Egger test (P = .98), Begg test (P = .81), or visual inspection of the funnel plot (Supplemental Fig 5; available at http://www.jaad.org).

Dose-response and duration-response analyses

In all, 6 studies evaluated the relationship between duration of voriconazole therapy and risk of SCC (Supplemental Table II).[7,19-21,25,26] Of those 6 studies, 5 found that duration of voriconazole use was significantly associated with the development of SCC,[19-21,25,26] whereas 1 found no such association.[7] Meta-analysis of 4 studies found that longer duration of voriconazole use was significantly associated with

Table I. Characteristics of the included studies

Study	Design and data source	No. of participants	Age, y	Selection criteria	Definition of exposure	Adjusted covariates
Vadnerkar et al, 2010[20]	Retrospective, case-control study; UPMC between 2003 and 2008; median follow-up, 36 mo	68 LTs; SCC cases, 17; control, 51	Median age of cases, 63; median age of controls, 56	Patients with an LT or heart-lung transplant	Cumulative doses and total durations of voriconazole use obtained from the UPMC pharmacy record and Cardiothoracic Transplant database, respectively	Older age at the time of transplant, male sex, residence in a location with high levels of sun exposure, single LT, and duration and cumulative dose of voriconazole
Feist et al, 2012[26]	Retrospective cohort study; University of California San Diego Health System between 2000 and 2006; follow-up, NR	120 LTs; with voriconazole, 43; no voriconazole, 77; SCC cases, 32	Mean age with voriconazole use, 49.4; with no voriconazole use, 48.6	Single LT bilateral sequential single (double) LT	Exposed to voriconazole	NR
Rashtak et al, 2015[7]	Retrospective cohort study; Mayo Clinic between 1990 and 2011; median follow-up, 3 y	166 LTs; SCC cases, 44; BCC cases, 19	Mean, 52	LT alone, heart-lung transplant, or lung-heart-liver transplant	NR	Univariate Cox models
Wojenski et al, 2015[19]	Retrospective cohort study; Mayo Clinic from 2007 to 2012; follow-up, NR	381 HSCTs; SCC cases, 27	Median, 53	Adult patients with an allogeneic HSCT	Intravenous or oral voriconazole use at any time during treatment of patients' hematologic disease, before or after HSCT	Male sex; age at time of transplant; total body irradiation conditioning; skin cancer before HSCT; chronic GVHD; photopheresis; UV therapy
Kolaitis et al, 2016[24]	Retrospective cohort study; University of California at Los Angeles between 2005 and 2012; follow-up, NR	400 LTs; SCC cases, 84	Mean, 59	Adult recipients of a first single LT or bilateral LT	Exposure to fungal prophylaxis was measured in 2 ways: (1) targeted and universal prophylaxis groups and (2) cumulative time-dependent exposure to specific medications	Patients' age at transplant, sex, race, diagnosis, transplant type, and time-dependent cumulative acute rejection score

Mansh et al, 2016[22]	Retrospective cohort study; University of California at San Francisco between 1991 and 2012; follow-up, NR	455 LTs; SCC cases, 86	Median, 55.4	Single LT, double LT, or heart-lung transplant	Exposed to voriconazole identified using medical record review	Sex, race (white vs nonwhite) and age at transplant
Hamandi et al, 2018[25]	Retrospective, cohort study; 14 LT centers across 9 countries during 2005-2008; Median follow-up, 3.51 y	900 LTs; SCC cases, 55	Median, 53	Adult patients with a single LT, double LT, or heart-lung transplant	Cumulative voriconazole exposure of ≧30 d, not necessarily consecutive	Age, sex, immunosuppression regimen, mean cyclosporine level, mean tacrolimus level, sun exposure, history of malignancy before transplantation, transplant rejection episodes, and underlying disease
Kuklinski et al, 2017[23]	Retrospective cohort study; Stanford Blood and Marrow Transplantation database between 2003 and 2015; follow-up, NR	1220 allogeneic HCTs; SCC cases, 60; BCC cases, 22	Mean, 9.2	Allogeneic HCT	Use of voriconazole either before or after HCT	Older age at the time of HCT, male sex, white race, and history of NMSC; chronic GVHD

GVHD, Graft-versus-host disease; *HCT*, hematopoietic cell transplant; *HSCT*, hematopoietic stem cell transplant; *LT*, lung transplant; *NR*, not reported; *UPMC*, University of Pittsburgh Medical Center; *UV*, ultraviolet.

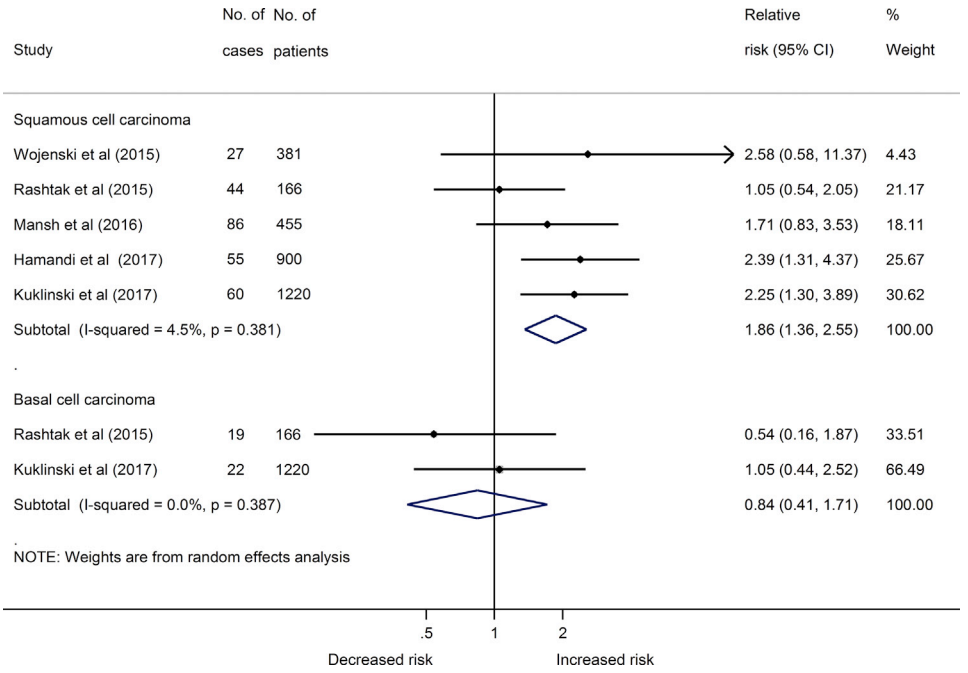

Fig 2. Meta-analysis of the association between voriconazole use and risk of squamous cell carcinoma and basal cell carcinoma. *CI*, Confidence interval.

increased risk of SCC (RR, 1.72; 95% CI, 1.09-2.72),[7,19,25,26] whereas a nonsignificant positive association was observed in cumulative days of voriconazole use (RR, 1.74 per 180 days; 95% CI, 0.95-3.18) (Supplemental Fig 6; available at http://www.jaad.org). In addition, 2 studies evaluating cumulative dose and risk of SCC reported a statistically significant dose-response relationship (Supplemental Table II).[22,25]

BCC risk

Two studies involving 41 BCC cases among 1386 patients (crude incidence, 3.0 %) were included in the meta-analysis.[7,23] Neither found any association between voriconazole use and risk of BCC. The overall RR was 0.84 (95% CI, 0.41-1.71) (Fig 2).

DISCUSSION

Our meta-analysis of observational studies found that voriconazole use was significantly associated with increased risk of SCC in both LT recipients and HCT recipients. Our sensitivity analysis omitting each study, 1 at a time, confirmed the robustness of our results. Cumulative meta-analysis indicated that the significant increase in the risk of SCC associated with voriconazole became robust beginning in 2017. Furthermore, longer duration or higher dose of voriconazole was associated with increased risk of SCC. However, there was no significant association between voriconazole exposure and risk of BCC.

Consistent with most previous studies,[19,20,22-26] our results found that voriconazole use was significantly associated with increased risk of SCC. Although the potential carcinogenic mechanisms by which voriconazole causes SCC have not been fully elucidated, it has been hypothesized that either voriconazole or VNO may facilitate UV-induced DNA damage and inhibit DNA repair.[18,30] Furthermore, VNO may cause phototoxicity through non−radiation-related mechanisms after exposure to UV B.[31-33] Because cytochrome P450 enzymes are expressed not only in the liver but also in human keratinocytes,[34] an accumulation of VNO in the skin may explain our findings that longer duration and higher dose of voriconazole were independent risk factors for SCC.[18] Sun exposure is more strongly related to the risk of SCC than to the risk of BCC.[35] Photosensitizing medications (eg, diuretics) were found to be more strongly associated with SCC than with BCC.[36] Therefore, it was not surprising that our study found no association between voriconazole and BCC, though this might also be a falsely negative finding resulting from the inclusion of only 2 studies. In addition, it should be noted that we observed a significant increase in the risk of SCC regardless of whether a study was adjusted for sun exposure. Thus, phototoxicity may not be the sole carcinogenic pathway involved. Some studies have found that voriconazole may promote tumor development by upregulating the aryl hydrocarbon

receptor–dependent COX pathway[33] and induce SCC by regulating distinct cell cycle and terminal differentiation pathways in human keratinocytes.[32]

Our study systematically searched all available cohort or case-control studies on voriconazole use and risk of SCC or BCC without any restriction (eg, language). Moreover, we fully assessed the methodologic quality of the included studies and provided separate outcomes for SCC and BCC. Finally, subgroup analysis, sensitivity analysis, cumulative meta-analysis, and dose-response analysis were performed to test the robustness of our findings.

Our meta-analysis had several limitations. First, the definition of voriconazole treatment varied considerably among studies, ranging from ever-exposure to at least 3 consecutive months of voriconazole therapy, which was undefined in many studies. Additionally, voriconazole was commonly used in combination with immunosuppressants in both LT recipients and HCT recipients. Immunosuppressants, especially azathioprine, were considered a strong risk factor for SCC.[37,38] However, because several studies did not provide details of treatment combinations, we could not address this issue in our study. One study, which was adjusted for immunosuppression regimen, mean cyclosporine level, and mean tacrolimus level, found a significant increase in the risk of SCC.[25] One included study found no association between any particular immunosuppressive medication and risk of skin cancer.[7] Further studies are clearly warranted to explore potential interaction between voriconazole and immunosuppressive therapies for skin cancer among those patients with an LT or HCT. Finally, some clinical factors, such as time since transplantation,[39] age at transplantation, skin type, and history of NMSC, might confound the relation between voriconazole use and SCC. However, we cannot further eliminate residual confounders on account of the limited number of studies included and the lack of information provided.

In summary, our systematic review and meta-analysis of 8 observational studies suggested a significant association between voriconazole use and increased risk of SCC among individuals who have undergone lung transplantation or hematopoietic cell transplantation. A trend toward dose-response and duration-response relationships was noted. The findings support the need for regular dermatologic surveillance for the patients taking voriconazole and also suggest that the alternatives to voriconazole (eg, posaconazole) be taken, especially by those already at elevated risk of SCC. Given the relatively limited data, further large, high-quality studies with more detailed exposure information in terms of dose and duration of voriconazole and adequate adjustment for potential confounders (eg, UV exposure) are required for confirmation of our findings.

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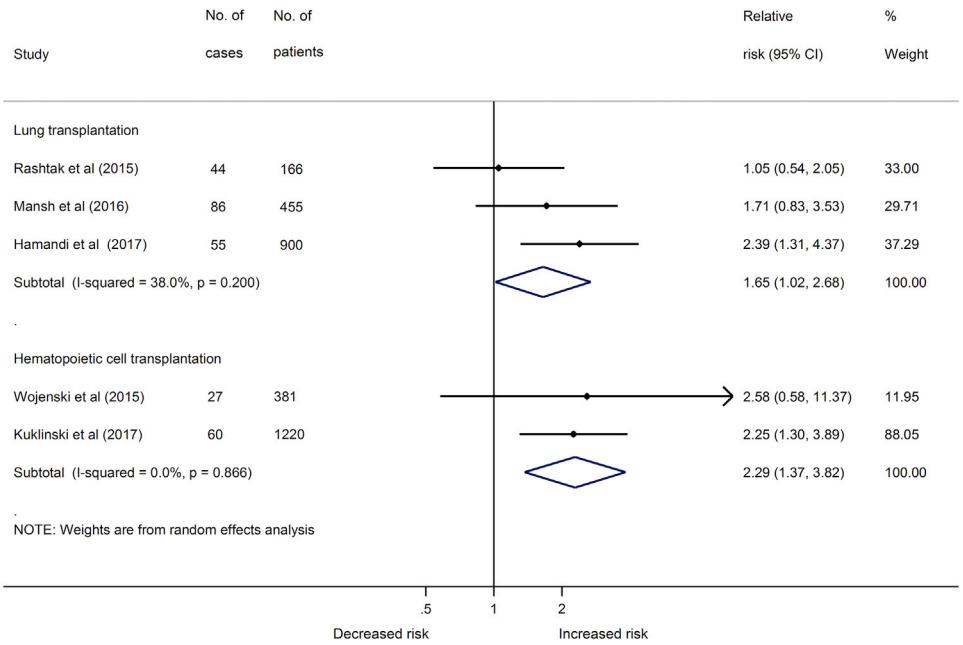
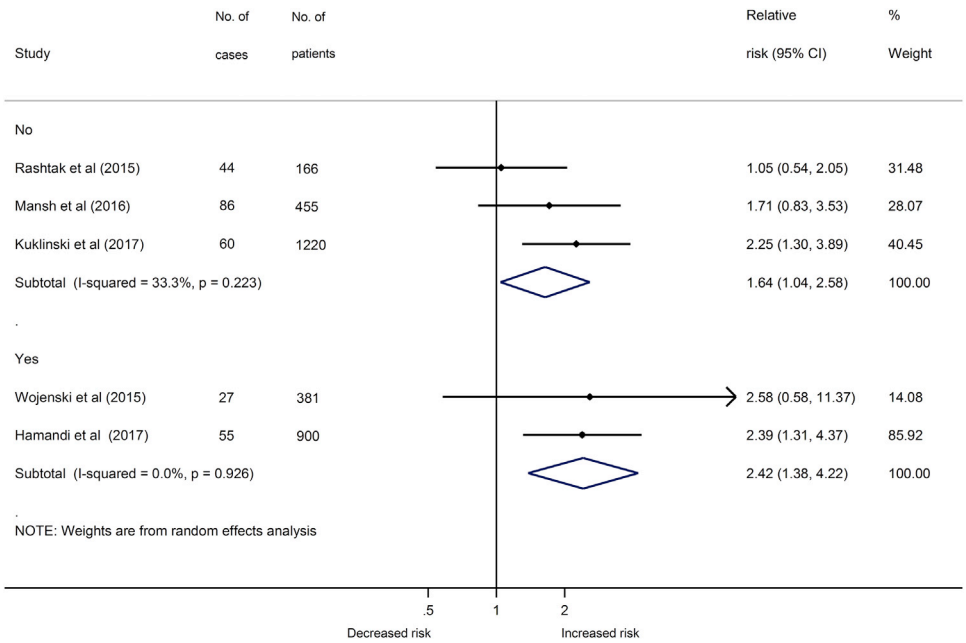
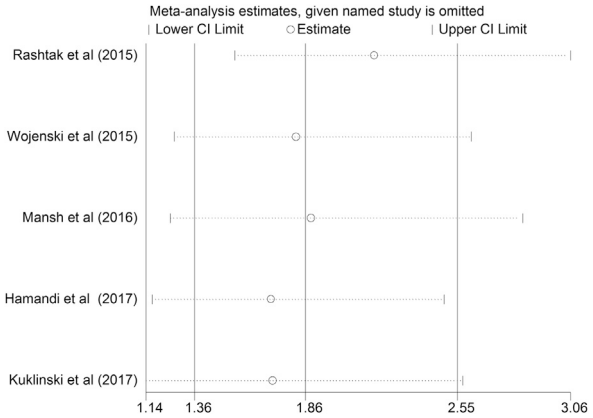


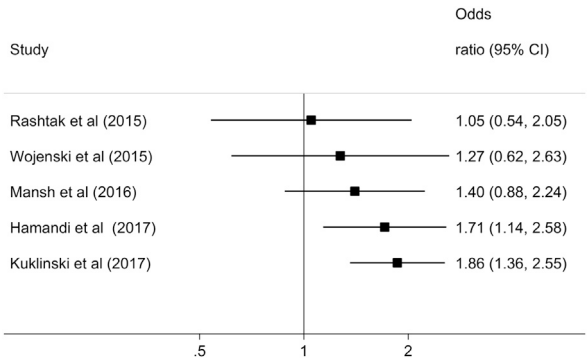
Supplemental Fig 1. Meta-analysis of the association between voriconazole use and risk of squamous cell carcinoma, stratified by type of transplantation. *CI*, Confidence interval.



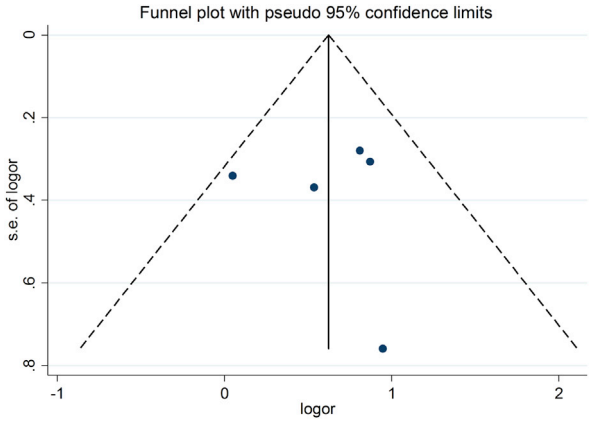
Supplemental Fig 2. Meta-analysis of the association between voriconazole use and risk of squamous cell carcinoma, stratified by adjustment for sun exposure. *CI*, Confidence interval.



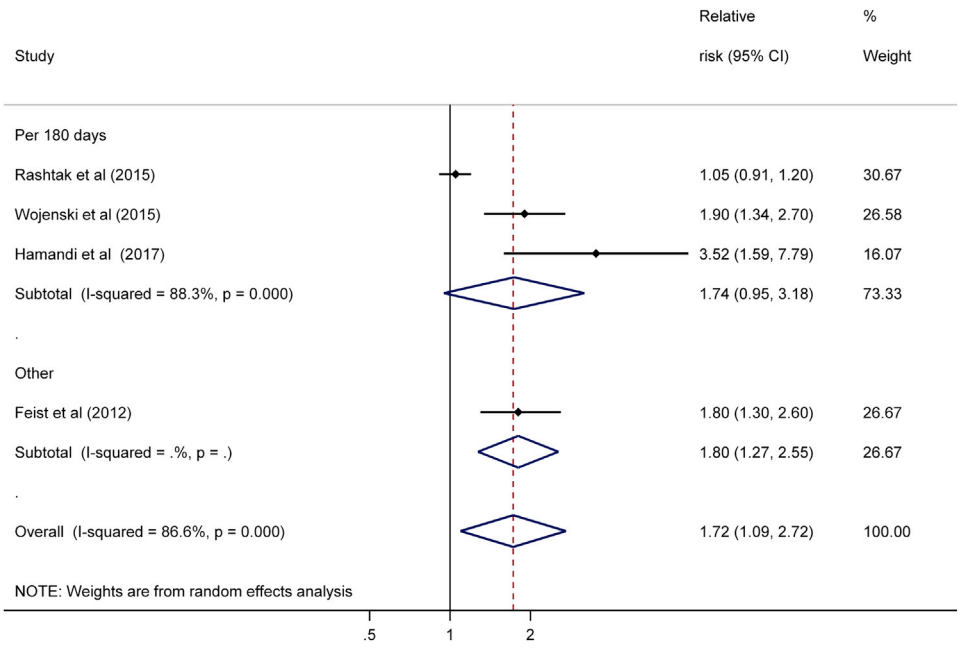
Supplemental Fig 3. Sensitivity analysis of the association between voriconazole use and risk of squamous cell carcinoma by removing 1 study at a time. *CI*, Confidence interval.



Supplemental Fig 4. Cumulative meta-analysis of the association between voriconazole use and risk of squamous cell carcinoma, based on year of publication. *CI*, Confidence interval.



Supplemental Fig 5. Visual inspection of the funnel plot of the association between voriconazole use and risk of squamous cell carcinoma. *logor*, Log of odds ratio.



Supplemental Fig 6. Meta-analysis of the association between voriconazole duration and risk of squamous cell carcinoma. *CI*, Confidence interval.

Supplemental Table I. Search strategy

Characteristic	Specification
Search date	September 2017
Databases	PubMed and Embase
Search terms	voriconazole and (skin cancer OR skin neoplas* OR squamous cell cancer OR squamous cell carcinoma* OR basal cell cancer OR basal cell carcinoma* OR SCC OR BCC OR non melanoma skin cancer OR nonmelanoma skin cancer OR NMSC or melanoma OR malignant melanoma OR keratinocyte cancer)
Restriction	None

BCC, Basal cell carcinoma; *NMSC*, nonmelanoma skin cancer; *SCC*, squamous cell cancer.

Supplemental Table II. Summary results of the included studies

Study	Squamous cell carcinoma	Basal cell carcinoma
Vadnerkar et al (2010)[20]	Univariate analysis: Duration of voriconazole use (P = .03) and cumulative dose (P = .03) Multivariate analysis: Duration of voriconazole use (HR = 2.1; P = .04)	
Feist et al (2012)[26]	Multiple logistic regression analysis: Duration of voriconazole use: OR, 1.8; 95% CI, 1.3-2.6; P = .001	
Singer et al (2012)[21]	Multivariable Cox models: Ever exposed to voriconazole vs never exposed: HR, 2.62; 95% CI,1.21-5.65; P = .014 This risk was dose dependent: the risk for SCC increased by 5.6% with each 60 d of exposure at a standard dose of 200 mg twice daily	
Rashtak et al (2015)[7]	Univariate Cox models: Exposure to voriconazole: HR, 1.05; 95% CI, 0.54-2.05; P = .888 Duration of voriconazole use (per 180 d): HR 1.05; 95% CI, 0.91-1.20; P = .522	Univariate Cox models: Exposure to voriconazole: HR, 0.54; 95% CI, 0.16-1.87; P = .332 Duration of voriconazole use: HR (per 180 d of exposure), 0.79; 95% CI, 0.53-1.18; P = .25
Wojenski et al (2015)[19]	Multivariable Cox models: Exposure to voriconazole: HR, 2.58; 95% CI, 0.58-11.37; P = .21 Cumulative days of voriconazole use (per 180 d): HR, 1.90; 95% CI, 1.34-2.70; $P < .001$	
Kolaitis et al (2016)[24]	Time to first SCC: Univariate analysis: HR, 1.62; 95% CI, 1.27-2.09; $P < .001$ Multivariate analysis: HR, 1.71; 95% CI, 1.33-2.20, $P < .001$	
Mansh et al (2016)[22]	Unadjusted Kaplan-Meier methods: Any exposure to voriconazole: HR, 1.91; 95% CI, 1.11-3.27; P = .02 Cumulative-dose exposure (per 12 g of exposure); HR, 1.02; 95% CI, 1.01-1.03; P = .001 Adjusted model: Any exposure to voriconazole: HR, 1.71; 95% CI, 0.83-3.53; P = .15 Cumulative-dose exposure (per 12 g of exposure): HR, 1.03; 95% CI, 1.02-1.04; $P < .001$	

Continued

Supplemental Table II. Cont'd

Study	Squamous cell carcinoma	Basal cell carcinoma
Hamandi et al (2018)[25]	Univariate analysis: Exposure to voriconazole: HR, 2.55; 95% CI, 1.42-4.60; *P* = .002 Multivariable model: Exposure to voriconazole: HR, 2.39; 95% CI, 1.31-4.37; *P* = .005 Adjusted time-dependent covariate: Mean daily dose of voriconazole (per 1 DDD increment): HR, 2.70, 95% CI, 1.53-4.78; *P* = .001 Adjusted, time-dependent covariates, by duration: No exposure to any azole: Ref Exposure to voriconazole 1-90 d: HR, 0.45, 95% CI, 0.10-2.10; *P* = .311 Exposure to voriconazole 91-180 d: HR, 2.23, 95% CI, 0.94-5.30, *P* = .07 Exposure to voriconazole >180 d: HR, 3.52; 95% CI, 1.59-7.79; *P* = .002	
Kuklinski et al (2017)[23]	Multivariate analysis: Exposure to voriconazole: HR, 2.25; 95% CI, 1.30-3.89; *P* = .004	Multivariate analysis: Exposure to voriconazole: HR, 1.05; 95% CI, 0.44-2.52; *P* = .913

CI, Confidence interval; *DDD*, defined daily dose *HR*, hazard ratio; *OR*, odds ratio; *Ref*, reference.

Supplemental Table III. Quality assessment of the included studies according to the Newcastle-Ottawa scale

Study	Design	No. of stars for selection (max = 4)	No. of stars for comparability (max = 2)	No. of stars for exposure/outcome (max = 3)	Total
Wojenski et al (2015)[19]	Cohort	3	1	2	6
Hamandi et al (2018)[25]	Cohort	3	2	2	7
Kolaitis et al (2017)[24]	Cohort	4	1	2	7
Kuklinski et al (2017)[23]	Cohort	3	1	2	6
Mansh et al (2016)[22]	Cohort	4	1	2	7
Rashtak et al (2015)[7]	Cohort	3	0	2	5
Feist et al (2012)[26]	Cohort	3	0	3	6
Vadnerkar et al (2010)[20]	Case-control	3	2	2	7

For case-control studies:
The study can be awarded 1 star if it meets the selection marked with a star (*) in each numbered item below. A maximum of 1 star can be given for each item within "selection" and "exposure"/"outcome" and maximum of 2 stars within "comparability."

Selection

1) Is the case definition adequate?: a) yes, with independent validation*; b) yes (eg, record linkage or based on self-reports); c) no description. 2) Representativeness of the cases: a) consecutive or obviously representative series of cases*; b) potential for selection biases or not stated. 3) Selection of controls: a) community controls*; b) hospital controls; c) no description. 4) Definition of controls: a) no history of disease (end point)*; b) no description of source.

Comparability

1) Comparability of cases and controls on the basis of the design or analysis: a) study controls for most important factor*; b) study controls for any additional factor.*

Exposure

1) Ascertainment of exposure: a) secure record (eg, surgical records)*; b) structured interview where blind to case-control status*; c) interview not blinded to case/control status; d) written self-report or medical record only; e) no description. 2) Same method of ascertainment for cases and controls: a) yes*; b) no. 3) Nonresponse rate: a) same rate for both groups*; b) nonrespondents described; c) rate different and no designation.

For cohort studies:

Selection

1) Representativeness of the exposed cohort: a) truly representative of the average, treated with voriconazole*; b) somewhat representative of the average, treated with voriconazole*; c) selected group of users (eg nurses, volunteers); d) no description of the derivation of the cohort. 2) Selection of the nonexposed cohort: a) drawn from the same community as the exposed cohort*; b) drawn from a different source; c) no description of the derivation of the non exposed cohort. 3) Ascertainment of exposure: a) secure record (eg, surgical records)*; b) structured interview*; c) written self-report; d) no description. 4) Demonstration that outcome of interest was not present at start of study: a) yes*; b) no.

Comparability

1) Comparability of cohorts on the basis of the design or analysis: a) study controls for the most important factor*; b) study controls for any additional factor.*

Outcome

1) Assessment of outcome: a) independent blind assessment*; b) record linkage*; c) self-report; d) no description. 2) Was follow-up long enough for outcomes to occur?: a) yes*; b) no. 3) Adequacy of follow-up of cohorts: a) complete follow-up*; b) subjects lost to follow-up were unlikely to introduce bias*; c) follow-up rate less than 80% and no description of those lost; d) no statement.

Max, Maximum.