**Category**: Clinical Research

**Title**: Syphilis and risk of cutaneous squamous cell carcinoma

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Abstract

**Background:** Squamous Cell Carcinoma (SCC) and Basal Cell Carcinoma (BCC) are the most common skin cancers in the United States, with SCC causing greater morbidity. Syphilis can trigger inflammation, ulceration, and scarring, potentially promoting carcinogenesis via immune dysregulation, ultraviolet (UV) sensitivity, and Toll-like receptor activation [1–4]. The link between syphilis and nonmelanoma skin cancer remains unclear.
**Objective:** To evaluate the 5-year risk of invasive cutaneous SCC and BCC in patients with syphilis.
**Methods:** We conducted a retrospective cohort study using deidentified electronic health records from the TriNetX research network. Patients with early syphilis (ICD-10 A51), late syphilis (A52), or any syphilis (A51–A53) were compared with matched controls. Individuals with prior photochemotherapy, photodynamic therapy, or UV therapy were excluded. Propensity score matching accounted for age, sex, race/ethnicity, immunosuppressant use, and history of irradiation. Five-year risks of invasive SCC (excluding SCC in situ) and BCC were evaluated. Outcomes before the 5-year window were excluded.
**Results:** Early syphilis was linked to a higher overall SCC risk (RR 2.043, 95% CI 1.471–2.837, P<.01), especially on the trunk (RR 4.407, 95% CI 2.218–8.755, P<.01) and head/neck (RR 2.175, 95% CI 1.328–3.563, P=.002). Extremity risk was not significant. Late syphilis increased SCC risk on the trunk (RR 2.151, 95% CI 1.266–3.656, P=.004) and extremities (RR 1.398, 95% CI 1.024–1.908, P=.034), with no significant overall or head/neck risk. No increases in BCC risk were observed.
**Conclusions:** Our preliminary findings suggest a possible association between syphilis and increased risk of invasive SCC, particularly on the trunk, while BCC risk was not increased. The truncal predominance aligns with secondary syphilitic eruptions, suggesting that mucocutaneous inflammation and scarring create a localized pro-tumorigenic environment. Observed relative risks are modest compared with high-risk groups, such as transplant recipients or individuals with a genetic predisposition to skin cancer. Limitations include ICD-10 coding, which does not capture infection stage, treatment, or disease duration, and the heterogeneity of syphilis, as patients without mucocutaneous involvement have different risk profiles [5]. Larger studies incorporating syphilis stage, treatment, and UV exposure are needed to establish syphilis as a definitive SCC risk factor.

References

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