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Title: Association Between Syphilis and Non-Melanoma Skin Cancer: A Retrospective Analysis

Background: Non-melanoma skin cancers, including squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), are the most common malignancies in the U.S., with SCC posing a higher morbidity risk. Despite syphilis cases rising nearly 80% in the past decade (2), its potential link to skin cancer remains unexplored. Syphilis, particularly secondary syphilis, causes inflammation, ulceration, and scarring. These effects, combined with TLR-2 and TLR-5 activation, chronic inflammation, immunosuppression similar to HIV, and increased UV sensitivity from skin damage, may contribute to skin cancer development. While no studies directly link syphilis to skin cancer, evidence from other chronic inflammatory skin conditions suggests a possible association. This study examines whether syphilis is associated with an increased risk of SCC or BCC in a large cohort.

Methods: This retrospective cohort study utilized TriNetX, a global research network with de-identified electronic health records, to evaluate 171,412 individuals diagnosed with syphilis (ICD10CM: A51-A53). These individuals were compared to 4,349,304 controls to assess the risk of developing non-melanoma skin cancers, specifically SCC and BCC, over 5 years. Patients with a history of photochemotherapy, photodynamic therapy, or ultraviolet therapy were excluded. Propensity score matching (PSM) was conducted using a 1:1 nearest-neighbor algorithm, matching age, sex, race/ethnicity, immunosuppressant use, and personal history of irradiation. Covariate balance was assessed using standardized differences, with all post-matching values <0.01, confirming the successful matching of 157,216 individuals per cohort. Outcomes of BCC and SCC were evaluated in total and across specific areas, including the head & neck, trunk, and extremities, with risk analysis excluding prior diagnoses of these cancers.

Results: For SCC, syphilis patients had a 27% increased risk for head & neck SCC (RR: 1.27, $p = 0.018$). The strongest association was for SCC of the trunk, where syphilis patients had a fourfold higher risk than controls (RR: 4.18, $p < 0.001$). SCC of the extremities showed a modest, non-significant increase (RR: 1.16, $p = 0.204$). Overall, syphilis patients had a 42% higher risk of SCC across all sites (RR: 1.42, $p < 0.001$). For BCC, no significant differences were observed. Head & neck BCC risk was similar between syphilis patients and controls (RR: 0.94, $p = 0.422$), as were BCC rates for the trunk (RR: 1.154, $p = 0.244$) and extremities (RR: 1.071, $p = 0.577$). Total BCC risk was slightly lower in syphilis patients (RR: 0.89, $p = 0.067$), but this was not statistically significant.

Conclusion: Syphilis is significantly linked to an increased risk of SCC, especially on the trunk and head & neck. No association was found between syphilis and BCC. These findings suggest

that syphilis-related immune dysregulation or chronic inflammation may contribute to skin cancer development. For syphilis patients, skin cancer risk assessments should be prioritized in infectious disease and dermatology care, with a particular focus on SCC on trunk lesions. Further research is needed to clarify the underlying mechanisms driving the syphilis-SCC association.