doi:10.36849/JDD.9381e

Benzoyl Peroxide Use is Not Associated with an Increased Risk of Skin Cancer: Findings from a Multicenter TriNetX Cohort Study

Neal Gupta MD,[a,b]* Fariha Hanif MPH,[b]* Maile Ray D.Sc MPH,[c,d] Ashley Shayya MPH,[c] Sandra McGinnis PhD,[c] Jared Jagdeo MD MS[a,b]

[a]Dermatology Service, Veterans Affairs New York Harbor Healthcare System - Brooklyn Campus, Brooklyn, NY
[b]Department of Dermatology, State University of New York, Downstate Health Sciences University, Brooklyn, NY
cCenter for Human Services Research, College of Integrated Health Sciences, State University of New York, University at Albany, Albany, NY
[d]Department of Health Policy, Management, and Behavior, College of Integrated Health Sciences, State University of New York, University at Albany, Albany, NY

*co-first authors

To the Editor,

Benzoyl peroxide (BPO) is a widely used over-the-counter topic agent for treating acne vulgaris; however, the recent findings of benzene, a known carcinogen, in some BPO products have raised concerns about its safety.[1,2] This study aims to assess the potential risk of skin cancer associated with BPO use in humans through a retrospective analysis.

Using data from the TriNetX US Collaborative Network, a network of 92 participating health organizations, we identified BPO exposure in patients who received a diagnosis of acne vulgaris between the ages of 12 and 70 years old and received at least 3 prescriptions containing either 2.5% or 5% BPO of any formulation. The 2.5% and 5% strengths, rather than the 10% strength, were selected to increase the likelihood of facial application of benzoyl peroxide in the exposed group. Patients who developed the outcomes of interest before the index date or within 5 years after the index date were excluded to minimize the inclusion of those with preexisting disease. This included patients with any pre-existing diagnosis code for skin cancer, benign tumors of skin, melanoma, and lipoma of the face or neck. A control comparator group was defined as patients diagnosed with acne vulgaris who had no record of receiving a prescription for benzoyl peroxide within their documented medical history between 2003 and 2024. To strengthen our results, we conducted two additional analyses using control groups of patients with seborrheic keratosis and seborrheic dermatitis, conditions associated with regular skin examinations but less commonly treated with BPO.

Outcomes of interest were limited to the face: the most common site of BPO application in the conditions studied. These outcomes included any cancer that affected the scalp, neck, ear, eyelid, or lip. The risks of various skin cancers were assessed including the risks of basal cell carcinoma, squamous cell carcinoma, and unspecified cancers of the face. In addition to cancerous outcomes, benign tumors of the face, melanocytic nevi, and lipoma were evaluated.

Propensity Score Matching (PSM) was performed for each of the three groups of exposed and control cohorts to minimize confounding and ensure comparability.[3] Matching was conducted using a 1:1 greedy nearest neighbor algorithm, based on demographic characteristics such as age, sex, race, and ethnicity. Further adjustments were made using ICD-10 codes, including nicotine dependence, alcohol use, and a family history of malignancy. Additionally, the cohorts were balanced based on usage of acne treatments such as isotretinoin, tretinoin, adapalene, and tazarotene. This adjustment accounts for the photosensitizing nature of these medications, which may have effects when combined with BPO.

TriNetX's "compare outcomes" feature was used to analyze the data. The index date for the exposed cohort was defined as the point when three prescriptions for BPO and a diagnosis of acne vulgaris were documented in a patient's record. The index date for the control cohort was set to when the diagnosis of acne vulgaris first appeared in a chart. The time window for analysis began 5 years after the index date and extended over a 15-year period. Cox proportional hazards models were applied to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). Censoring was applied to patients who were lost to follow-up or did not experience the outcomes of interest by the end of the study.

There was no significant difference observed in the rate of skin cancers among patients prescribed BPO compared to those without a BPO prescription, with an HR of 0.15 (95% CI: 0.04,0.56). A statistically significant decrease in the risk of benign tumors

doi:10.36849/JDD.9381e

of the face was observed with an HR of 0.64 (95% CI: 0.47,0.86). To account for possible OTC use of BPO in acne patients, an additional analysis was performed using the comparator cohort of patients with seborrheic keratosis.[4] This analysis revealed a significant decrease in the risk of skin cancer of the face among patients exposed to BPO with an HR of 0.10 (95% HR: 0.03,0.30).

An analysis comparing acne patients treated with BPO to those with seborrheic dermatitis revealed a reduced risk of skin cancers of the face, with an HR of 0.06 (95% CI: 0.01,0.29). A nonsignificant reduction in the risk of benign tumors of the face was also observed in this comparison, with an HR of 0.88 (95% CI: 0.53,1.46).

This study provides evidence that BPO use in acne treatment is not associated with an increased risk of skin cancer. Further prospective studies should investigate these findings further and assess the long-term safety profile of BPO across diverse populations and settings. Future research could also apply this methodology to other dermatological conditions such as hidradenitis suppurativa. These insights are essential for ensuring that BPO, a widely used acne treatment, continues to be safely incorporated into routine dermatological care.

DISCLOSURES

No funding has been received for this article.The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the U.S. Department of Veterans Affairs or the United States Government.

ACKNOWLEDGMENT

Jared Jagdeo formulated the hypothesis. Neal Gupta performed the literature search, database search, and wrote the report. Fariha Hanif helped edit the main report. Maile Ray, Ashley Shayya, Sandra McGinnis helped formulate the methodology, review, analyze, and interpret database results, and review and edit the manuscript. Jared Jagdeo helped edit/review the final manuscript. All authors reviewed and approved the final manuscript.

Statements and Declarations

No funding has been received for this article.The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the U.S. Department of Veterans Affairs or the United States Government.

REFERENCES

1. Leyden JJ. Therapy for acne vulgaris. *N Engl J Med.* 2001;344(15):1156-1162. doi:10.1056/NEJM200104123441507
2. Slaga TJ, Klein-Szanto AJ, Triplett LL, et al. Skin tumor-promoting activity of benzoyl peroxide, a widely used free radical-generating compound. *Science.* 1981;213(4511):1023-1025. doi:10.1126/science.6791284
3. Zhang Z, Kim *HJ, Lonjon G, et al. Balance diagnostics after propensity score matching. Ann Transl Med.* 2019;7(1):16. doi:10.21037/atm.2018.12.10. PMID: 30788363; PMCID: PMC6351359.
4. Roldán-Marín R, Becker JC, Stockfleth E. Actinic keratosis and keratolytic therapy: prevention of skin cancer by removing hyperkeratotic lesions. *Dermatol Ther.* 2016;6(1):35-49. doi:10.1007/s13555-016-0166-x.

AUTHOR CORRESPONDENCE

Jared Jagdeo MD MS
E-mail:..... jrjagdeo@gmail.com