Association of elevated transferrin saturation with lower prevalence of skin cancer diagnosis among adults: analysis of the third National Health and Nutritional Examination Survey (NHANES III)

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Background

- **Hemochromatosis** (H, formerly hereditary hemochromatosis) is a genetic disorder leading to systemic iron overload.[1] Most H patients in the United States (US) are of European descent and have homozygous C282Y mutations in the HFE gene.[2] Excess iron has carcinogenic effects in the liver, though its effects in the skin are less studied and potentially different by skin cancer type.[3]
- Among H patients, a single-center US study reported an increased likelihood of basal cell carcinoma (BCC), whereas European studies found no association with squamous cell carcinoma (SCC), BCC, or melanoma.[4-6]
- These conflicting results may be influenced by iron's beneficial role in promoting melanoma cell-death through **ferroptosis**, a non-apoptotic process mediated by buildup of lipid peroxides in cell membranes.[7-8]

Objective

- No national-scale study exists on the prevalence of skin cancer among H individuals in the US.
- Elevated transferrin saturation (TS) is a screening tool for H. We reasoned that elevated TS could be used as an indicator of iron-overload and a proxy for H.[9]
- Our study uses nationally representative data from NHANES III to investigate the association of elevated TS with the prevalence and likelihood of skin cancer diagnosis among adults in the US.

- **How does the likelihood of skin cancer change when TS is elevated?**
- **How does the association of skin cancer and elevated TS change between participant demographic groups?**

Methods

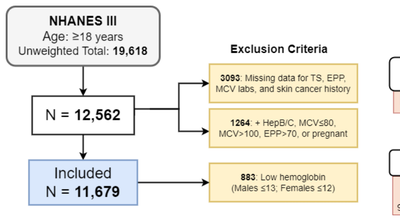

Fig 1. Patient selection criteria.

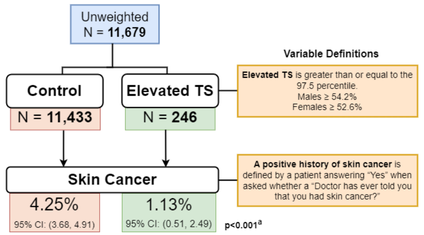

Fig 2. Criteria for elevated TS and skin cancer history

- NHANES III data does not differentiate between or exclude types of skin cancer.[10]

- [a] Comparative analysis of the estimate weighted prevalence of participants with skin cancer history performed using the **χ2 test** with second order Rao-Scott correction.
- **Survey-weighted multivariable logistic models** predicted odds ratios (OR) and average marginal estimates (AME) on a probability-scale for skin cancer history.

Results

1 **Iron parameters among participants with elevated TS**

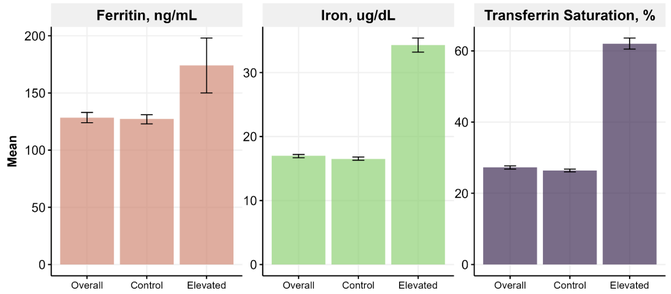

Fig 3. Iron parameters of patients with and without elevated transferrin saturation (TS).

Results (continued)

2 **Skin cancer probability decreases when TS is elevated, especially for older individuals**

Fig 4. AME differences in the probability of skin cancer throughout age among individuals with and without elevated TS.

3 **Decrease in skin cancer probability is most pronounced among Non-Hispanic Whites with elevated TS.**

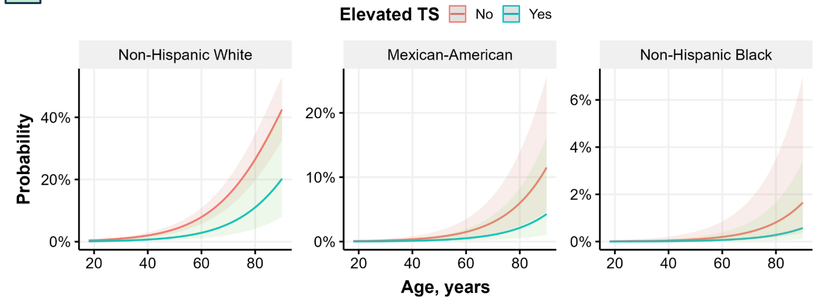

Fig 5. AME differences in the probability of skin cancer among racial-ethnic groups with and without elevated TS.

4 **Group differences in the Marginal Effect of TS on Skin Cancer**

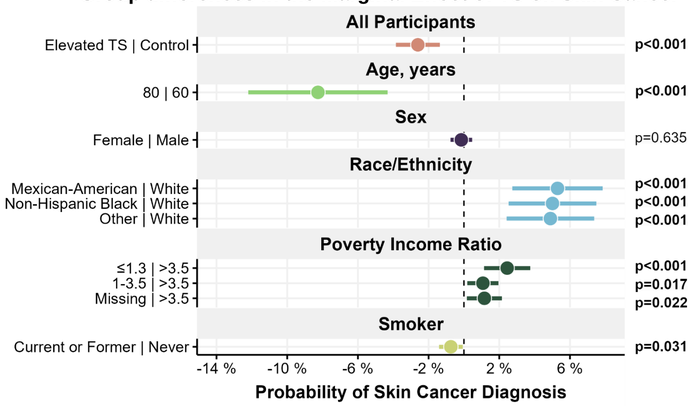

Fig 6. AME differences in the probability of skin cancer among patient demographics.

Discussion

Study criteria for elevated TS potentially identifies C282Y homozygotes

- Prior genotypic analysis of NHANES III participants revealed that Non-Hispanic Whites had the highest prevalence of H (C282Y homozygotes).[2]
- Our study reports a 2.46% (95% CI: 2.08, 2.91) estimated weighted prevalence of participants meeting criteria for elevated TS, while genotypic analysis reported a 0.26% (95% CI: 0.12, 0.49) prevalence of C282Y homozygotes and a 1.89% (95% CI: 1.48, 2.43) prevalence of H63D homozygotes.[2]

Race Influences the Association of Elevated TS and Skin Cancer Probability

- Elevated TS was associated with decreased skin cancer probability compared to patients without elevated TS.
- Comparing racial-ethnic groups, this decrease in skin cancer probability was more pronounced for non-Hispanic Whites with elevated TS.
- Factors influencing this result include the iron-mediated ferroptosis of cancerous cells or photoprotection of the skin by deposited iron pigment.

Age-Based Differences

- Older participants with elevated TS had a decreased probability of skin cancer compared to younger participants with elevated TS.
- Temporal accumulation of iron stores in the body may increase the likelihood that older individuals with HH have a higher degree of iron overload compared to those that are younger.
- This difference may be further influenced by the higher proportion of menopausal females among older participants.
- Menstrual blood loss may mitigate iron overload for pre-menopausal females. Group differences in skin cancer probability may exist among females with elevated TS based on menopausal status.[11]

Poverty Income Ratio (PIR) may predict lower likelihood of venesection

- Compared to patients with a PIR greater than 3.5, elevated TS was associated with the greatest decrease in skin cancer probability among patients with a PIR of 1.3 or lower.
- Prior studies report increased likelihood of BCC among H patients with a history of phlebotomy treatment compared to those with no history.[4]
- H patients with a lower PIR may be less likely to undergo phlebotomy due to financial constraints, leading to a higher degree of iron overload and an associated decrease in skin cancer probability compared to patients with a higher PIR.[12]

Conclusion

- Skin cancer is less likely among individuals with elevated TS, especially among Non-Hispanic Whites.
- The prevalence of homozygous H participants is highest among Non-Hispanic Whites.
- Our criteria for elevated TS utilizing the 97.5 percentile may have utility in the large-scale identification of H individuals homozygous for C282Y or H63D mutations.
- This retrospective cross-sectional study provides a hypothetical framework for understanding the likelihood and relative prevalence of skin cancer among individuals with iron-overload.
- These results add evidence to iron's potential to mitigate the development and metastasis of skin cancer.
- Future studies are needed to investigate differences among skin cancer types (melanoma versus NMSC) in the association of iron overload and likelihood of skin cancer, and to identify genetic mutations related to iron metabolism that may influence this association.

References

1. Adams PC. Acta Haematol. 2009;122(2-3):134-139.
2. Steinberg KK, et al. JAMA. 2001;285(17):2216-2222.
3. Elmberg M, et al. Gastroenterology. 2003;125(6):1733-1741.
4. Pan CX, et al. JAAD. 2023;88(3):692-694.
5. Atkins JL, et al. Cancer Epidemiol Biomarkers Prev. 2022;31(9):1780-1787.
6. Barry R, et al. Br J Dermatol. 2023;188(Supplement_4):ljad113.199.
7. Liu L, et al. Front Cell Dev Biol. 2023;10:1079648.
8. Tally R, Bosenberg M. Pigment Cell Melanoma Res. 2022;35(1):18-25.
9. Asberg A, et al. Scand J Gastroenterol. 2001;36(10):1108-1115.
10. Plan and operation of the Third National Health and Nutrition Examination Survey, 1988-94. Series 1: programs and collection procedures. Vital Health Stat Ser 1 Programs Collect Proced. 1994;(32):1-407.
11. Moirand R, et al. Ann Intern Med. 1997;127(2):105-110.
12. Casanova-Esteban P, et al. Metabolism. 2011;60(6):830-834.

Commercial Support Information

The authors have no commercial support of this project to disclose.