Uncovering Drug-Associated Skin Cancer Patterns Through Machine Learning

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Background / Significance:

This study investigated the association between frequently prescribed medications, particularly in combination, and skin cancer risk using the All of Us Database v8.

Objective:
To assess the cumulative skin cancer risk associated with long-term use and combinations of up to six commonly prescribed drugs, especially those with photosensitizing or vasoactive effects.

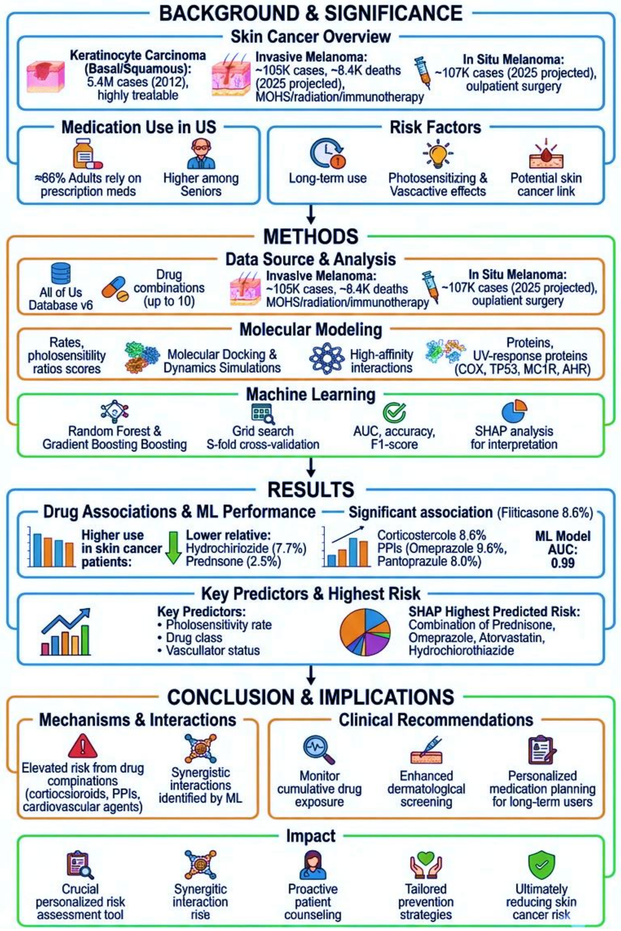
Skin Cancer Cases and Deaths in the U.S.

Type of Skin Cancer	Estimated Cases	Year	Treatment
Keratinocyte Carcinoma*	5.4 million cases **	2012	Highly treatable through surgeries, occasional metastasis
Invasive Melanoma	104,960 cases	2025	Can be comprised of MOHS surgery, lymph node surgery, and radiation/immunotherapy
In Situ Melanoma	107,240 cases	2025	Usually an outpatient surgery
Melanoma Deaths	8,430 deaths	2025	

Table 1. *Estimated incidence and mortality of skin cancer in the United States. While keratinocyte carcinoma* (basal and squamous cell carcinoma) is the most diagnosed form, it is not tracked by cancer registries; therefore, this is an estimated value from a study conducted in 2012. Invasive melanoma, though less common, causes most skin cancer deaths. In situ melanomas are early-stage, emphasizing the critical role of early detection. (Cancer Facts & Figures 2025, American Cancer Society.)*

- Approximately 66% of adults in the US rely on prescription medications, with this percentage significantly increasing among senior citizens.
- Risk: drug photosensitizing & vasoactive effects → potential skin cancer link

Methods



Results

Classification	Drug Name
Blood Pressure Medications	
Vasodilator/Ca Channel Blocker	Amlodipine
Thiazide Diuretic	Hydrochlorothiazide
Alpha- and Beta-Blocker	Carvedilol
ACE Inhibitor	Lisinopril
Angiotensin II Receptor Blocker	Losartan
Beta-Blocker	Metoprolol
Antidepressants	
SNRI	Duloxetine
SSRI	Fluoxetine
SSRI	Escitalopram
SSRI	Sertraline
Cholesterol-Lowering Agents	
HMG-CoA Reductase Inhibitor	Atorvastatin
HMG-CoA Reductase Inhibitor	Simvastatin
HMG-CoA Reductase Inhibitor	Rosuvastatin
CNS Stimulant	
MAO Inhibitor	Amphetamine
Hormone Replacement	
Thyroid Hormone Supplement	Levothyroxine
Gastrointestinal Agents (PPIs)	
PPI	Omeprazole
PPI	Pantoprazole
Corticosteroids	
Inhaled Corticosteroid	Fluticasone
Systemic Corticosteroid	Prednisone
Antidiabetic	
Biguanide	Metformin
Analgesic / Antipyretic	
COX Inhibitor	Acetaminophen
Respiratory	
Leukotriene Receptor Antagonist	Montelukast

Table 2. Drugs of Interest. *This table presents a categorized list of the commonly prescribed medications in the United States that are associated with suspected or confirmed photosensitivity side effects. Drugs were selected based on prescribing frequency data from ClinCalc DrugStats and the Medical Expenditure Panel Survey (MEPS). Groupings reflect general therapeutic classifications.*

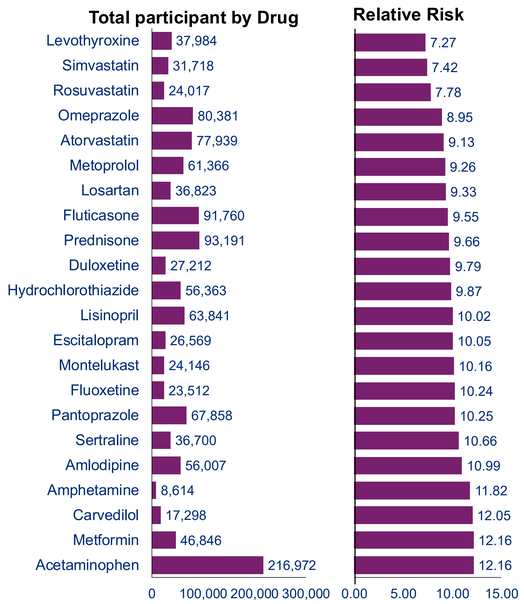


Figure 2. *Number of participants considered in the study from the All of Us v8 database who reported using each of the drugs of interest. Acetaminophen was the most frequently used drug, with over 216,000 users, followed by Prednisone and Fluticasone. These participant counts form the basis for subsequent skin cancer risk modeling and photo-sensitivity contribution analysis.*

Figure 3. *RR of developing malignant skin cancer for each of the drugs of interest, as determined by a ML model. Higher values indicate greater predicted association with skin cancer. Acetaminophen, Metformin, and Carvedilol were associated with the highest relative risks,*

Comparison of Model Predictions with Observed Drug-Linked Cancer Data

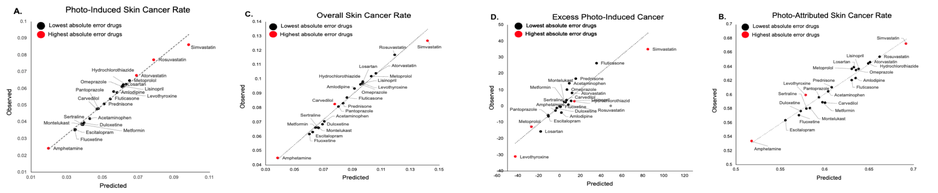


Figure 4. *This series of plots compares predicted versus observed values for four drug-specific cancer risk metrics across commonly prescribed medications. Each dot's position relative to the regression line reflects model accuracy.. Color intensity indicates absolute error—black dots show low prediction error, while red dots show high prediction error. This visualization identifies high-error outliers and evaluates the model's performance for each metric.*

Comparative Docking Scores and Glide Energies of Selected Drugs Against COX2 and AHR

		Atorvastatin	Prednisone	Omeprazole	Hydrochlorothiazide
COX2	Score	-11.40	-5.8	-5.6	-3.4
	Glide emodel	-98.623	2.678	-61.911	-34.53
AHR	Score	-4.3	-4.2	-3.9	-2.4
	Glide emodel	-44.800	-29.674	-35.809	-27.310
TP53	No interactions				
MC1R	No interactions				

Table 5*. Docking scores, OPLS energy, and Glide model values for atorvastatin, prednisone, omeprazole, and hydrochlorothiazide against COX2 and AHR proteins. TP53 and MC1R showed no detectable interactions under the applied docking conditions.*

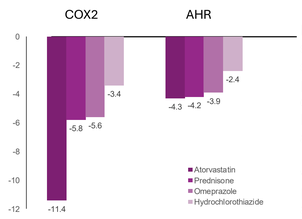


Figure 5a: Bar plot showing the docking scores of atorvastatin, prednisone, omeprazole, and hydrochlorothiazide against COX2 and AHR targets. More negative values indicate stronger predicted binding affinity.

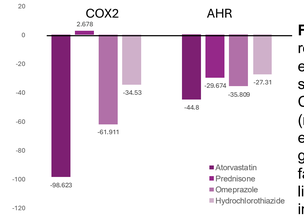


Figure 5b: Bar plot representing the Glide energy values of the same drugs docked to COX2 and AHR. Lower (more negative) Glide energy values reflect greater energetic favorability of the ligand–protein interactions.

Drug-Level Associations with Photosensitivity-Linked Skin Cancer Risk

Drug Name	Connections	SC/PS Gap (%)
Levothyroxine	Photosensitivity may not be the primary cause	42.11
Simvastatin	Partial contribution from photosensitivity	30.80
Rosuvastatin	Partial contribution from photosensitivity	33.80
Omeprazole	Partial contribution from photosensitivity	36.47
Atorvastatin	Partial contribution from photosensitivity	39.91
Metoprolol	Partial contribution from photosensitivity	36.96
Losartan	Partial contribution from photosensitivity	36.70
Fluticasone	Partial contribution from photosensitivity	36.96
Prednisone	Partial contribution from photosensitivity	39.18
Duloxetine	Photosensitivity may not be the primary cause	42.68
Hydrochlorothiazide	Partial contribution from photosensitivity	35.07
Lisinopril	Partial contribution from photosensitivity	36.15
Escitalopram	Photosensitivity may not be the primary cause	44.40
Montelukast	Photosensitivity may not be the primary cause	41.66
Fluoxetine	Photosensitivity may not be the primary cause	42.86
Pantoprazole	Photosensitivity may not be the primary cause	40.61
Sertraline	Photosensitivity may not be the primary cause	42.05
Amlodipine	Partial contribution from photosensitivity	36.50
Amphetamine	Partial contribution from photosensitivity	34.89
Carvedilol	Photosensitivity may not be the primary cause	48.19
Metformin	Photosensitivity may not be the primary cause	40.25
Acetaminophen	Partial contribution from photosensitivity	39.59

Table 3. *This table displays the drugs of interest and the potential role of photosensitivity in contributing to skin cancer risk, utilizing a Gap% metric from the All of Us Research Program v8 dataset. A higher Gap%, represented by blue, suggests that skin cancer may occur through non-photosensitive mechanisms (e.g., immunosuppression or metabolic effects), whereas a lower Gap%, represented by red, implies a potential link between drug-induced photosensitivity and cancer development.*

Drug combination	RR	AR
Lisinopril_Omeprazole_Pantoprazole	8.43	0.37
Atrovastatin_Prednisone_Hydrochlorothiazide_Omeprazole	7.20	0.37
Acetaminophen_Fluticasone_Hydrochlorothiazide	8.42	0.37
Duloxetine_Carvedilol_Omeprazole	8.18	0.37
Acetaminophen_Rosuvastatin	7.36	0.36
Rosuvastatin_Amphetamine	9.30	0.34
Acetaminophen_Prednisone_Omeprazole	7.33	0.33
Acetaminophen_Duloxetine_Metoprolol_Amphetamine	7.38	0.32
Fluoxetine_Pantoprazole	9.27	0.29
Acetaminophen_Fluoxetine	9.43	0.28
Metformin_Montelukast	10.18	0.26
Fluoxetine_Rosuvastatin_Amlodipine_Levothyroxine	5.92	0.25
Escitalopram_Rosuvastatin_Levothyroxine	3.87	0.24
Escitalopram_Simvastatin_Losartan_Levothyroxine	3.86	0.24
Escitalopram_Sertraline_Amphetamine_Fluticasone	10.04	0.23

Table 4*. This table highlights drug combinations most strongly associated with elevated skin cancer risk. Relative Risk (RR) indicates how many times more likely skin cancer is in users of the listed combinations compared to those not using them, while Absolute Risk (AR) reflects the direct proportion of affected individuals. The red combinations have high RR and AR values, suggesting a stronger and more clinically meaningful association..*

Comparative Ligand Binding and Interaction Landscapes of AHR & COX2

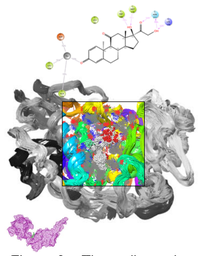


Figure 6a :Three-dimensional visualization of ligand binding within the AHR pocket,

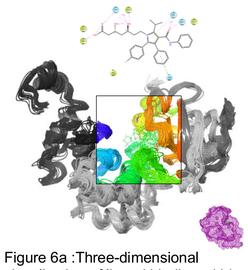
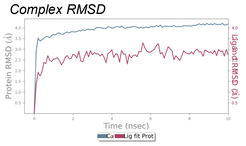
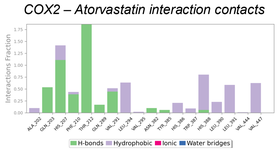


Figure 6a :Three-dimensional visualization of ligand binding within the COX2 pocket,

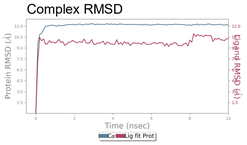
COX2 Protein and Atorvastatin Complex RMSD



COX2 – Atorvastatin interaction contacts



AHR Protein and Atorvastatin Complex RMSD



AHR – Atorvastatin interaction contacts

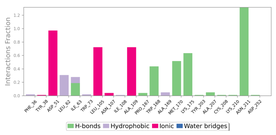


Figure 7a–d. Molecular dynamics analysis of atorvastatin bound to COX2 and AHR. **(7a–b)** show RMSD stability and residue-wise interaction contacts for the COX2–atorvastatin complex, (7c–d) present the corresponding RMSD profiles and interaction distributions for the AHR–atorvastatin complex, highlighting key stabilizing interactions during the simulation.

CONCLUSIONS and IMPLICATIONS

Key Findings & Mechanistic Insight

- Combined use of commonly prescribed drugs—including proton pump inhibitors (PPIs), corticosteroids, and cardiovascular agents—is associated with a higher risk of skin cancer.
- This elevated risk appears to be driven by synergistic effects of photosensitivity and vasodilation, amplifying UV-induced skin damage.
- Machine learning (ML) models identified photosensitivity rating, drug class, and vasodilator status as strong predictors of skin cancer, achieving an AUC of 0.89.
- SHAP analysis pinpointed the highest-risk drug combination as prednisone, omeprazole, atorvastatin, and hydrochlorothiazide.

Mechanism of Observed Risk

Photosensitizing drugs absorb UV or visible light, entering an excited chemical state that initiates two major damaging pathways:

- **Reactive oxygen species (ROS)** – oxidize lipids, proteins, and DNA
- **Free radicals** – trigger DNA and cellular damage through electron transfer

These pathways lead to cellular injury, mutations, and ultimately, an increased risk of UV-induced skin cancer. Additionally, vasodilatory medications may intensify this effect by increasing skin blood flow and UV exposure.

Limitations	Future Work
Lifestyle, behavioral, geographic, skin color, and UV exposure were not available in the All of Us database	Integrate findings into EHR alerts or clinical risk assessment tools
Causal relationships cannot be inferred from observational data	Screen patients regularly who are prescribed high-risk medication combinations
Over-the-counter (OTC) drug usage was not captured	Expand the model to include other cancers, drug categories, and diverse populations
Risk model performance may vary across healthcare settings and populations.	Collaborate with dermatologists, geriatricians, and pharmacists for personalized prevention strategies
	Validate findings in prospective studies with more granular lifestyle and behavioral data
	Develop patient education tools that raise awareness about medication-induced photosensitivity