Prevalence of UV Mutational Signatures Among Cutaneous Primary Tumors

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Introduction

UV radiation exposure causes a characteristic genomic mutational pattern associated with elevated tumor mutational burden (TMB) via the formation of pyrimidine-pyrimidine photodimers (COSMIC signature 7). This signature is highly specific to UV-mediated mutagenesis, suggests cutaneous origin in cancers of uncertain primary site, and may also flag potential misdiagnoses by conventional histopathological examination. This principle has been used to support cutaneous origin for what had previously been termed primary pulmonary melanoma, but broader pan-cancer analyses are...
limited. Here, we examined the frequency of UV signatures in a pan-cancer next-generation sequencing (NGS) database.

**Methods**

Approval for this cross-sectional study, including a waiver of informed consent and Health Insurance Portability and Accountability Act waiver of authorization, was obtained from the Western Institutional Review Board. This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

We retrospectively analyzed all solid tumors submitted to Foundation Medicine for comprehensive genomic profiling between December 2013 and June 2021. NGS was performed using hybrid-capture as previously described. Mutational signature calling was performed using the decomposition method of Zehir et al using the 96-feature single-base substitution COSMIC reference signatures (version 2, March 2015) generated by Alexandrov et al, in which signature 7 is

**Figure 2. Genomic Alterations Associated With UV Radiation-Mediated Mutagenesis**

Detection of a UV signature was associated with genomic alterations typical of cancers occurring on sun-exposed skin, including nonacral cutaneous melanoma (e.g., BRAF [OR, 9.9; 95% CI, 9.5-10.4], NF1 [OR, 6.9; 95% CI, 6.5-7.2], NRAS [OR, 13.9; 95% CI, 13.1-14.7]), squamous cell carcinoma (NOTCH1 [OR, 5.9; 95% CI, 5.6-6.2], NOTCH2 [OR, 6.9; 95% CI, 6.5-7.2], NOTCH3 [OR, 8.6; 95% CI, 8.2-9.1], PTEN [OR, 1.4; 95% CI, 1.3-1.5], and PIK3CA [OR, 0.8; 95% CI, 0.8-0.9]), and basal cell carcinoma (PTCH1 [OR, 6.3; 95% CI, 5.9-6.6], SMO [OR, 4.0; 95% CI, 3.7-4.4], SUFU [OR, 5.4; 95% CI, 4.8-6.0]) (P < .0001 for all comparisons with Bonferroni correction, Fisher exact test). Alterations in TERT, TP53, CDKN2A, and RBL were frequent throughout the cohort. TMB indicates tumor mutational burden.
considered the UV signature, to yield coefficient weights representing the contributions of the signatures in each sample.4-6 At least 10 variants were required for signature analysis, which included all predicted somatic point variants with unknown functional status. TMB, quantified in mutations per megabase (mt/Mb), was determined on up to 1.1 Mb of DNA. Statistical tests were 2-sided and used a significance threshold of $P < .05$.

**Results**

Among 343,589 tumors, each from a different patient, 73,944 (21.5%) had sufficient mutations for signature analysis, of which 8143 tumors (11.0%) exhibited UV signatures (median [IQR] TMB, 31.3 [15.0-61.3] mt/Mb). Among the full cohort, the median (IQR) patient age was 63.0 (54.0-71.0) years, and 189,139 patients (55.0%) were women. Of 8143 tumors with UV mutational signatures, 4181 (51.3%) were submitted as tumors of primary cutaneous origin (3229 melanomas, 584 squamous cell carcinomas [SCCs], 191 basal cell carcinomas, 148 Merkel cell carcinomas, 82 angiosarcomas, 38 adnexal carcinomas, and 31 other mesenchymal neoplasms). Therefore, detection of a UV signature supported the diagnosis. In addition, 2765 tumors (34.0%) were submitted as tumors without a specified primary site (2150 melanomas, 228 SCCs, 147 carcinomas not otherwise specified, 64 neuroendocrine carcinomas, 33 adenocarcinomas, 7 sarcomas, and 136 other neoplasms). Detection of a UV signature in these tumors raised the possibility of cutaneous origin and a more precise tumor classification. Most interestingly, 1075 tumors (13.2%) were submitted as tumors of extracutaneous origin; thus, detection of a UV signature raised the possibility of an occult cutaneous primary and suggested the potential for reclassification on further clinicopathologic evaluation (Figure 1). Potentially misclassified tumors included 314 lung cancers, 168 sarcomas (including 28 malignant peripheral nerve sheath tumors and 3 clear cell sarcomas), 126 salivary gland cancers, 121 nonsalivary head and neck cancers, 54 breast cancers, 14 urothelial cancers, and 278 other neoplasms. Detection of a UV signature, regardless of a clinical diagnosis of cutaneous, unspecified, or extracutaneous origin, was associated with genomic alterations typical of cancers occurring on sun-exposed skin, including nonacral cutaneous melanoma ($\text{BRAF}, \text{NF1}, \text{NRAS}$), squamous cell carcinoma ($\text{NOTCH1/2/3}, \text{PTEN}, \text{PIK3CA}$), and basal cell carcinoma ($\text{PTCH1}, \text{SMO}, \text{SUFU}$) (Figure 2). Alterations in $\text{TERT}, \text{TP53}, \text{CDKN2A}$, and $\text{RB1}$ were frequent throughout the cohort.

**Discussion**

This retrospective cross-sectional study of 343,589 patients with solid tumors represents the largest pan-cancer genomic survey of UV mutational signatures conducted to our knowledge. Among 73,944 tumors suitable for mutational signature analysis, identification of a UV signature served as a useful biomarker for identifying cancers of potential cutaneous origin with important implications for clinical management. Although associated clinical data were not always available for direct review, in many cases, reclassification would be expected to affect pathologic and clinical stage, including primary vs metastatic status, as well as therapy selection.

Limitations of this study include its retrospective nature, a lack of follow-up data, and the requirement for at least 10 mutations for signature analysis. Nevertheless, this study provides compelling evidence that NGS-based UV mutational signature analysis could refine the primary site in cancers of uncertain origin and suggest alternative diagnoses in tumors initially classified as extracutaneous. Therefore, this method provides a complementary tool to the standard histological and immunohistochemical workup, with important implications for clinical management.