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An Update on Skin Cancers and Sun Exposure

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Abstract: ***By 1927 for basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), and by 1955 for melanoma, the broad grounds for relating sun exposure to skin cancer had been established: that these are more frequent in residents of areas of high ambient solar irradiance, are more frequent in sun-sensitive people, occur mainly on sun-exposed body sites, are more frequent in people with high sun exposure, and are more frequent in people with benign sun-related skin conditions. Both quantity and quality to the epidemiological evidence and, most recently, provided direct evidence that sun exposure is the cause of mutations in critical tumor suppressor genes in BCC, SCC and melanoma. Complete or more convincing answers are still needed to many questions of detail. They include whether the pattern of sun exposure is really important in, and acts independently of amount of sun exposure in, affecting the risk of melanoma and BCC; the relationship between the amount of sun exposure and risk of BCC and melanoma is when the pattern of exposure is held constant; whether there really is a plateau in risk of BCC and melanoma beyond some level of the amount of exposure; whether this exposure-response relationship depends on cutaneous sensitivity to the sun and in what way; whether sunburn makes a specific contribution to the risk of skin cancer independent of the amount of sun exposure; whether sun exposure close to the time of diagnosis of skin cancer contributes anything to the development of the cancer; what the solar radiation action spectrum is for each kind of skin cancer; and whether sunscreens are effective in protecting against skin cancer.***

Keywords: Skin Cancer, Basal Cell Carcinoma BCC, Squamous Cell Carcinoma SCC, melanoma, UV radiation, Sun exposure

1. Introduction

Exposure of the skin to solar ultraviolet (UV) radiation has both risks and benefits for human health. Absorption of UV-B radiation by DNA results in mutations that underlie the development of skin cancers, as is apparent from genetic studies showing high occurrence of UV signature mutations within these tumors. UV-B radiation is also absorbed by 7-dehydrocholesterol to initiate vitamin D synthesis. In experimental studies vitamin D metabolites enhance apoptosis of malignant cells, inhibit angiogenesis and proliferation and increase differentiation, potentially reducing skin cancer development and improving prognosis after diagnosis.

2. Skin Cancer Incidence, Mortality, Burden & Cost

Accurate incidence rates are hard to capture for the keratinocyte cancers, squamous cell carcinoma and basal cell carcinoma.Fatality rates for keratinocyte skin cancers are low, but approximately 55,000 deaths result from melanoma each year.Skin cancers cause a significant health burden and cost to healthcare systems.Of note, however, a recent publication suggests that, an apparent decrease is seen when dark skin immigrants where included. A recent analysis has shown that after adjustment for age, sex and the levels of ambient UV radiation, the average annual increases in SCC and BCC incidence were 4 and 1%, respectively.Despite the challenges, there is strong evidence that KC incidence has increased markedly in the last several decades.

UV radiation & skin cancer

There is considerable evidence showing that exposure to the sun causes skin cancer, including from observations of geographical variation in incidence, a higher risk in people with fair skin, an increased risk in people with markers of actinic damage such as actinic keratoses and the presence within tumors of 'UV-signature' genetic mutations (cytosine to tyrosine transitions at cyclobutane pyrimidine dimers).

Table 1: UV signature mutation spectrum in all samples

Mutation type	C>T transitions at dipyrimidinic sites across all samples (YC:RG>YT: RA) except tandem base substitutions (CC:GG>TT:AA)	Tandem base substitutions at CC sites across all samples (CC:GG>TT:AA), each counted as 2	Total "UV Signature" (Ikehata and Ono, 2011)
Number	18,212	2,440	20,652
Mean proportion of coding mutations	66.70%	8.90%	*75.70%*

G>T (oxidative) and T>G (UVA fingerprint) are not included here because of their uncertain UV origins.

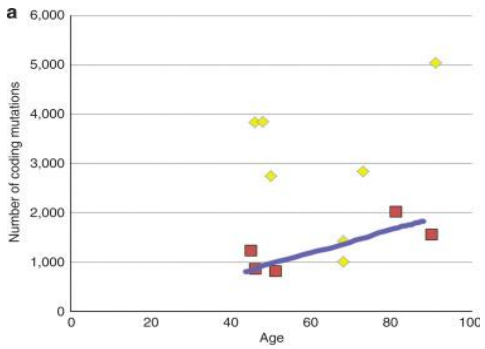

Figure (a) Number of coding mutations versus age and photo exposure; each data point represents one tumor. There is a slight trend (blue line) of increasing mutation rates with age in tumors from "protected" (intermittently sun-exposed) parts. Mutations rates are higher in chronically sun-exposed versus intermittently sun-exposed parts (yellow vs. red data points).

Exposure to UV-A radiation causes free radical production, resulting in oxidative damage.Exposure to UV-B radiation induces DNA damage; recent genetic studies confirm many UV 'signature mutations' in skin cancers, including both driver and bystander mutations.UV-induced immunosuppression results from irradiation in both UV-A and UV-B wavelengths and is an important factor in skin cancer development.

Despite the difficulties in ascertaining the true incidence of KCs, there is a strong association between KC incidence and intensity of ambient ultraviolet radiation (UVR). In a recent quantitative review restricting the analysis to fair-skinned populations only, intensity of ambient UVR accounted for almost 40% of the variability in incidence of SCC and BCC (with age, sex and calendar year additional important factors).The difference in incidence of skin cancers (including CMM and KC) between fair- and dark-skinned populations living in the same geographic location clearly illustrates the importance of skin type.

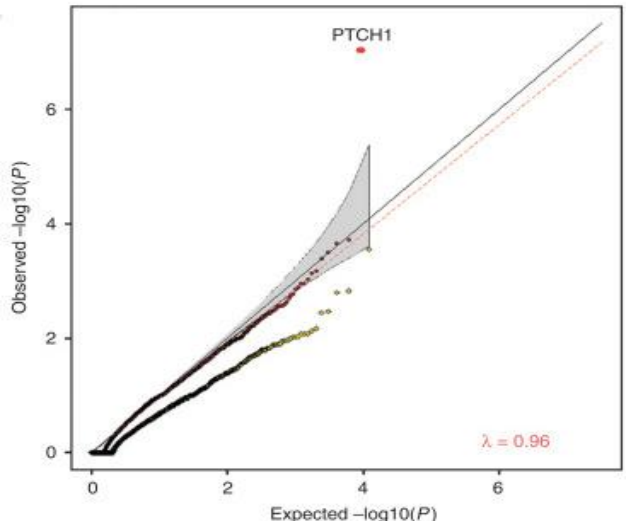

Figure (b) Q-Q plot of functional mutation burden test and synonymous mutation burden test across all genes with at least 1 mutation in the set of 12 tumors. Gray-shaded area represents 95% confidence intervals for expected *P*-values. Red points: functional mutation burden; yellow points: synonymous mutation burden.

Recent meta-analyses have also confirmed that greater numbers of naevi and atypical naevi, and the presence of actinic damage and KC are strong risk factors for CMM. In a recent report, there was a threefold increase in the risk of developing CMM after either SCC or BCC, even after adjustment for skin phototype. Chronic sun exposure may be more important for nodular BCC commonly found on the head and neck, and intermittent sun exposure more important for BCCs on the trunk.

Vitamin D, skin cancer risk & prognosis

Exposure to the sun causes both skin cancer and vitamin D production. Cutaneous production of vitamin D is initiated by exposure to UV-B radiation.Serum concentrations of 25-hydroxyvitamin D (25(OH) D) of 50 nmol/l or higher are classed as sufficient.Studies exploring the relationship between skin cancer risk and vitamin D show mixed results.Results from human studies are consistent in reporting that low levels of 25(OH)D are associated with thicker cutaneous malignant melanomas or a poorer prognosis.

What to tell skin cancer patients

Caution should be taken to avoid harmful levels of sun exposure.It is important to maintain vitamin D levels above 50 nmol/l. Patients at high risk of skin cancer should routinely apply sunscreen to the face, hands and arms. Areas less frequently exposed to UVR may be exposed for short periods (e.g., 10 min) in the middle of the day when the UV-B levels are highest.

3. Materials and Methods

Clinical samples:

All BCC samples and peripheral blood collected and sequenced in this study were done under protocols approved by the Institutional Review Board of Los Angeles Biomedical Research Institute. "Declaration of Helsinki" Principles were followed and patients gave their written informed consent before enrollment and sample collection. Only tumors with >80% tumor area on histological section were chosen for exome sequencing. DNA was extracted using the Roche MagnaPure automated system (Switzerland).

4. Conclusion

It is difficult, on the evidence to date, to provide any definitive answers on whether vitamin D has any protective role in skin cancer development or prognosis. Higher 25(OH)D levels postdiagnosis and higher sun exposure prediagnosis have been associated with thinner CMM and better prognosis, but it is impossible to tell how indicative the postdiagnostic 25(OH)D levels are of the prediagnostic situation. On the other hand, there is clear evidence that sun exposure increases the risk of all types of skin cancers. On the basis of the evidence reviewed here, it is prudent to

avoid high dose sun exposure leading to sunburn, to always protect the face and hands when in the sun, and to use sun protection when outdoors for other than short periods of time when the UVI is 3 or higher. It is important to maintain 25(OH)D levels of around 50 nmol/l or higher, and in many locations this should be achievable with short periods of sun exposure during the middle of the day in most seasons, with additional intake of vitamin D possibly required in winter in some locations.

Declaration of Conflicting Interest

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