Pancreatic Cancer is More Common than Melanoma in Non-White *CDKN2A* Positive Individuals

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Background and Aim:

Germline pathogenic and likely pathogenic variants (P/LPV) in *CDKN2A* predispose carriers to early onset melanoma and pancreatic cancers, however, cancer incidence and penetrance estimates have been derived primarily from White cohorts. We describe the incidence of melanoma and pancreatic cancers (PC) for individuals with *CDKN2A* P/LPV by ethnicity.

Methods:

Individuals with *CDKN2A* P/LPV identified at a single diagnostic laboratory from Jan 2012-Nov 2023 were characterized by age, self-reported ethnicity, and melanoma/PC diagnosis. This was performed for any *CDKN2A* P/LPV and specifically for the high-frequency Hispanic LPV, p.I49T. The rate of cancer diagnosis was compared to consecutively tested *BRCA2* positive individuals (positive controls) and pan-cancer panel (28-32 genes) negative individuals (wild type controls) identified from an overlapping time period (2012-2016).

Results:

A total of 1,286 individuals with P/LPV in *CDKN2A* were identified. Melanoma diagnoses were significantly decreased for non-White individuals (4.3%) when compared to White individuals (31%; $p<0.001$). There were no significant differences in PC between ethnicities, and on average PC was more common (6.7%) than melanoma in non-White individuals. A comparison of the Hispanic allele, p.I49T (n=479), revealed a 4.3-fold increase in PC (7.3%) compared to the wild type controls (1.8%; n=31,599)(95% CI 3.0-6.2; $p<0.001$) and a 1.8-fold increase compared to BRCA2 positive controls (4.1%; n=826)(95% CI 1.1-3.0; $p=0.01$).

Conclusions:

This work demonstrates that while the frequency of PC was consistent across all ethnic groups, melanoma was significantly less common for non-White individuals with a *CDKN2A* P/LPV compared to White individuals. PC may be the predominant tumor observed in non-White *CDKN2A* populations. This result is significant, as melanoma is considered major criteria for *CDKN2A* testing and *CDKN2A* variant interpretation. This indicates that non-White individuals may be undertested for *CDKN2A* and that causal pathogenic *CDKN2A* alterations may be under-identified. *CDKN2A* c.146T>C, p.I49T was shown to have a 4x increased risk in the development of PC and should be considered a high-risk allele.