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A functional variant in the immune signalling receptor NKG2D alters skin cancer risk

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Dear Editor,

Immune surveillance for the recognition and removal of abnormal cells is a key component of skin cancer prevention. Natural Killer (NK) cells are a front-line defense for the removal of aberrant cells. Considerable inter-individual variation in NK cell levels and cytotoxicity may alter skin cancer risk. Nearly four decades ago Hershey et al demonstrated that NK cells from melanoma patients and their family members had lower levels of cytotoxicity than healthy controls (1). Genetic variation contributes to this phenotypic variation, and a coding polymorphism in the Natural Killer Group 2 member D (NKG2D) receptor (rs2255336 in gene *KLRK1*) tracks with low and high NK cytotoxicity (HNK) phenotypes and reduced risk of several non-cutaneous cancers (2, 3).

The Skin Health Study of Minnesota is a population-based case-control study of invasive cutaneous melanoma (4). The New Hampshire Health Study is a population-based case-control study of keratinocyte skin cancer (5). We utilized the resources of these two studies to test the hypothesis that rs2255336 is associated with the three major forms of skin cancer. The high activity genotype (HNK/HNK) was inversely associated with melanoma (OR 0.52, 95% CI 0.30–0.95). We observed a similar, non-statistically significant association with BCC (OR 0.68, 95% CI 0.44 – 1.06), and no overall association with SCC (OR 0.82, 95% CI 0.49 – 1.38). These data from population-based studies support the hypothesis that NKG2D high cytotoxicity phenotype enhances immune surveillance in the skin and decreases risk of cutaneous cancers, most clearly for melanoma.

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Conflicts of interest: none to declare.

Despite the genotype-phenotype association observed for rs2255336 and NK cell killing, this variant has not emerged as a GWAS signal in studies of cancer, including skin cancers. We probed the Michigan Genomics Initiative (MGI) data using the Michigan PheWeb tool (6) and observed that rs2255336 is associated with SCC (p=0.03), and BCC (p=0.06) but not melanoma (p=0.3). These results are inconsistent with our study which found that rs2255336 is associated with melanoma and BCC, but not SCC. Epidemiologic methods may explain these differences. Namely, our studies are population-based while the MGI participants represent individuals undergoing surgery at University of Michigan hospitals, which would likely bias towards advanced stage skin cancer. In addition, the comparison group from MGI may not be an appropriate control group for skin cancer analyses. We feel these differences in participant selection (population-based vs high-risk surgical) likely explain the discrepancy between our results and those of the MGI.

NK cell levels and activity are known to vary by sex, therefore we tested for potential gene*sex interaction in our population-based studies. There was no evidence for interaction in melanoma (p=0.73). However, there was a pattern of interaction that was similar for both BCC (p=0.13) and SCC (p=0.03). The HNK/HNK genotype was associated with the expected skin cancer risk reduction in males (BCC OR=0.46, SCC OR=0.58). However, among females the HNK/HNK genotype increased the odds of keratinocyte skin cancer, which was particularly evident for SCC (OR=1.96). Interactions between sex and NKG2D ligands have previously been reported, suggesting possible estrogen-dependent immunomodulation differences (7). Continued study of innate immune variation by sex is warranted

Collectively our data lend further epidemiological support for an important role of innate immune cells in skin cancer development and suggest that this biology may differ by sex for keratinocyte cancers. NKG2D, as its name implies, is primarily understood in the context of NK cell signalling. While NK cells are not abundant in the skin, innate-like γδ T cells also express NKG2D and are important in immune surveillance in the skin. It should be noted that tumors exploit NKG2D biology for immune evasion. Specifically, tumors shed NKG2D ligands into the extracellular space, and these soluble ligands prevent synapse binding between innate immune cells and the tumor surface (8). Future studies should include examination of the highly polymorphic NKG2D ligands, known to fine tune NKG2D responses, to help clarify the role of the NKG2D receptor system on development of skin cancer.

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Table 1.

Association between rs2255336, a tagging SNP for high Natural Killer cell activity (HNK), and skin cancer.

	LNK/LNK	LNK/HNK	HNK/HNK	p-value
Melanoma				
Controls	509	241	34	
Cases	572	306	21	
OR (95% CI)	1.0 (reference)	1.12 (0.91 – 1.38)	0.57 (0.33 – 1.00)	<0.04
OR (95% CI)[1]	1.0 (reference)	1.10 (0.89 – 1.38)	0.52 (0.30 – 0.95)	<0.05
OR men (95% CI)[2]	1.0 (reference)	1.15 (0.82 – 1.62)	0.69 (0.28 – 1.66)	0.47
OR women (95% CI)[2]	1.0 (reference)	1.07 (0.80 – 1.43)	0.43 (0.20 – 0.94)	0.07
BCC				
Controls	674	344	51	
Cases	754	387	39	
OR (95% CI)	1.0 (reference)	1.01 (0.84 – 1.21)	0.67 (0.43 – 1.03)	0.21
OR (95% CI)[3]	1.0 (reference)	1.01 (0.85 – 1.21)	0.68 (0.44 – 1.06)	0.21
OR men (95% CI)[4]	1.0 (reference)	0.97 (0.76 – 1.23)	0.46 (0.25 – 0.84)	<0.03
OR women (95% CI)[4]	1.0 (reference)	1.06 (0.81 – 1.40)	1.16 (0.59 – 2.30)	0.85
SCC[3]				
Controls	674	344	51	
Cases	517	249	38	
OR (95% CI)	1.0 (reference)	0.89 (0.70 – 1.13)	0.73 (0.44 – 1.21)	0.85
OR (95% CI)[5]	1.0 (reference)	0.89 (0.70 – 1.14)	0.82 (0.49 – 1.38)	0.55
OR men (95% CI)[6]	1.0 (reference)	0.80 (0.61 – 1.04)	0.58 (0.32 – 1.03)	<0.05
OR women (95% CI)[6]	1.0 (reference)	1.23 (0.88 – 1.74)	1.96 (0.90 – 4.28)	0.29

[1] Model adjusted for age, sex, number of moles, cumulative UV exposure, and ever use of indoor tanning

[2] adjusted model stratified by sex

[3] Model adjusted for age, sex, and tendency to sunburn

[4] adjusted model stratified by sex

[5] Model adjusted for age, sex, tendency to sunburn and beta-HPV antibodies

[6] adjusted model stratified by sex