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A GWAS of cutaneous squamous cell carcinoma - Letter

Alice S. Whittemore[1], **Wei Wang**[1], **Eric Jorgenson**[2], and **Maryam M. Asgari**[2,3]

[1]Stanford University School of Medicine, Department of Health Research and Policy, Redwood Building, Stanford, California

[2]Division of Research, Kaiser Permanente Northern California, Oakland, California

[3]Department of Dermatology, Massachusetts General Hospital, Boston, Massachusetts

We read with interest the paper by Siiskonen and colleagues describing a genome-wide association study (GWAS) of cutaneous squamous cell carcinoma (cSCC) among individuals of European ancestry (1), which reported cSCC associations with variants at five genetic loci, based on data from 1,276 cSCC patients and 13,356 control subjects. Here we report a comparison of these results with those of a previous GWAS involving 7,701 non-Hispanic White (NHW) cSCC patients and 60,186 NHW control subjects in the Kaiser Permanente Northern California (KPNC) health care system (2).

The five loci reported by Siiskonen et al are located within or near genes on chromosomes 5, 6, 8, 16 and 20. We reviewed the regressions of cSCC against KPNC subjects' genotypes for the variant alleles identified at these five loci, and found support only for the variant in the *DEF8* gene on chromosome 16. None of the four remaining variants were associated with cSCC; per-risk-allele odds-ratios (ORs) ranged between 0.98 and 1.03, and all P-values exceeded 0.20. A standard power calculation based on the reported variant allele frequencies and ORs suggests that the KPNC data had essentially 100% statistical power to detect cSCC association at these four loci, if the associations were present.

The KPNC data confirm the reported association for the intronic single nucleotide polymorphism (SNP) rs8063761 in the *DEF8* gene, which encodes an activator of intracellular signal transduction. For this SNP, Siiskonen et al reported a per-risk-allele OR of 1.34 (95% confidence interval (CI) 1.22–1.47, $P = 1.7\times10^{-9}$) and we found an OR = 1.30 (CI =1.25–1.35, $P = 6.2\times10^{-43}$). However, rs8063761 did not maintain genome-wide statistical significance in the KPNC data after adjusting for the most strongly associated SNP in the region, which was the intronic SNP rs4268748 in *DEF8* (OR = 1.33 (CI= 1.28–1.39), $P = 1.8\times10^{-44}$). rs4268748 is associated with expression levels of *CDK10*, a gene critical for cell cycle progression in both sun-exposed and non-sun-exposed skin (3). As noted by Siiskonen et al, the role of both these SNPs in cSCC is complicated by their proximity to the skin pigmentation gene *MC1R*. Indeed, three SNPs in *MC1R* met genome-wide significance in the KPNC data, although none did so after adjustment for rs4268748.

Corresponding Author: Alice S. Whittemore, Stanford University School of Medicine, Department of Health Research and Policy, Redwood Building, Room T204, Stanford, CA 94305-5405. Tel: 650-723-5460; Fax: 650-725-6951; alicesw@stanford.edu.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

In summary, comparison of results from these two studies indicates the need for further work on the functions of selected SNPs in *DEF8* and *MC1R* to elucidate their potential causal roles and mechanisms in cSCC.

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