Null Results in Brief

Lack of Associations of Selected Variants in Genes Involved in Cell Cycle and Apoptosis with Skin Cancer Risk

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Introduction

Cell cycle regulation and apoptosis are essential defenses against cancer. Functional relevance of some germ line variants in cell cycle and apoptosis genes has been evaluated and inconsistent results have been reported on the associations between these variants and a number of cancer sites. The genotoxic effect of sunlight exposure has been shown in the etiology of both melanoma and nonmelanocytic skin cancer (1). UV radiation is capable of causing a wide range of lesions in DNA. UV-induced DNA damage can cause cell cycle arrest and apoptosis (2). We evaluated selected variants in genes involved in cell cycle and apoptosis (STK15, cyclin D1, p73, and caspase-8) with skin cancer risk in a nested case-control study within the Nurses’ Health Study.

Materials and Methods

We conducted a nested case-control study within the Nurses’ Health Study. Eligible cases in this study consisted of women with incident skin cancer from the subcohort who gave a blood specimen in 1989-1990 (n = 32,826), including squamous cell carcinoma and basal cell carcinoma cases with a diagnosis anytime after blood collection up to June 1, 1998 and melanoma cases (including 33 lentigo maligna and 77 in situ cases) up to June 1, 2000 with no previously diagnosed skin cancer. Detailed information about this study (219 melanoma, 286 squamous cell carcinoma, 300 basal cell carcinoma, and 873 control cases) up to June 1, 2000 with no previously diagnosed skin cancer. Detailed information about this study (219 melanoma, 286 squamous cell carcinoma, 300 basal cell carcinoma, and 873 controls) has been reported previously (3). Information on skin cancer risk factors was obtained from the prospective biennial questionnaires and the retrospective supplementary questionnaire. A cumulative lifetime sun exposure while wearing a bathing suit for each individual was developed by combining the UV database and the information obtained from the supplementary questionnaires. We constructed a multivariate confounder score to create a constitutional susceptibility score, summarizing natural skin color, natural hair color, child or adolescent tendency to burn, and the number of palpably raised moles on arms. We used this score to define women the constitutional susceptibility.

Genotyping assays were done by the 5′ nucleic assay (TaqMan) using the ABI Prism 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA). Genotyping was done by laboratory personnel blinded to case-control status, and blinded quality control samples were inserted to validate genotyping procedures; concordance for the blinded samples was 100%. We used a common control series in data analysis to increase statistical power. Unconditional logistic regression was employed to calculate odds ratio (OR) and 95% confidence interval (95% CI) to assess the risks of the three types of skin cancer. All statistical tests were two sided.

Results

A detailed description of the characteristics of cases and controls in the skin cancer nested case-control study was reported elsewhere (3). The genotype distributions of the five single-nucleotide polymorphisms were in Hardy-Weinberg equilibrium among controls. No significant associations were observed for the five polymorphisms with the three types of skin cancer (Table 1). We also explored the potential synergistic effects of the five polymorphisms by examining the associations of the number of these variant alleles carried and skin cancer risk. This exploratory analysis suggested a combined effect of these genetic variants in melanoma skin cancer development (OR of melanoma for ≥4 variants, 1.61; 95% CI, 0.96-2.69). No significant interactions were observed between these genetic variants and constitutional susceptibility score, the number of lifetime severe sunburns which blistered, and cumulative lifetime sun exposure while wearing a bathing suit.

Discussion

Our data do not support the hypothesis that these variants in cell cycle and apoptosis genes are associated with skin cancer risk. STK15 participates in cell cycle regulation from G2 to M phase. The Ile allele of the F311I polymorphism in STK15 was more effective in transforming rat cells to a more malignant phenotype (4). The results of a meta-analysis for 15 studies of cancer at multiple sites combined were significant for cancer risk in both heterozygotes (OR, 1.10; 95% CI, 1.03-1.18) and homozygotes (OR, 1.40; 95% CI, 1.22-1.59; ref. 5). In a hospital-based case-control study of 236 nonmelanocytic skin cancer cases and 182 controls, heterozygotes had an OR of 0.86 (95% CI, 0.57-1.29) and homozygotes showed an OR of 1.48 (95% CI, 0.49-4.46; ref. 5).

Cyclin D1 is involved in the transition from G2 to S phase. The A allele of the G241A polymorphism generates the truncated protein with a longer half-life (6). In a nested case-control study from Sweden and Finland of 197 basal cell carcinoma cases and 548 controls, the OR for heterozygotes was 1.11 (95% CI, 0.73-1.68) and that for homozygotes was 1.46 (95% CI, 0.90-2.36; ref. 7).
The p73 gene is a member of p53 family and induces G1 cell cycle arrest and apoptosis. Two linked polymorphisms, G4A and C14T, may influence the efficiency of translation initiation (8). The caspase-8 gene is involved in the initiation of apoptosis. No report has been published on the associations between the p73 C14T and the caspase-8 D285S polymorphisms and skin cancer risks.

In summary, we did not find evidence for associations between the selected variants in cell cycle and apoptosis genes and the risks of melanoma and nonmelanocytic skin cancer, nor were the associations modified by constitutional susceptibility score, lifetime severe sunburns, cumulative sun exposure, and risk of skin cancer.

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