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The *XRCC1* Arg399Gln Polymorphism, Sunburn, and Non-melanoma Skin Cancer: Evidence of Gene-Environment Interaction[1]

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ABSTRACT

XRCC1, a protein directly involved in the repair of DNA base damage, contains at least three common polymorphisms. One of these, the codon 399 arg→gln variant, has been associated with several cancer-related biomarkers, suggesting it may have functional significance in exposure-induced cancers. However, results from case-control studies have yielded conflicting results. We investigated the *XRCC1* arg399gln polymorphism and its interaction with carcinogen exposure in a large, population-based case-control study of non-melanoma skin cancer. Cases were derived from an incident survey of all newly diagnosed non-melanoma skin cancer in New Hampshire, and controls were population based and frequency matched to cases on age and sex ($n = 1176$). Exposure information was derived from a detailed interviewer-administered questionnaire, and *XRCC1* genotype was determined from blood-derived DNA using a PCR-RFLP method. Overall, the *XRCC1* homozygous variant gln399gln genotype was related to a significantly reduced risk of both basal cell [BCC; odds ratio (OR) 0.7, 95% confidence interval 0.4–1.0] and squamous cell carcinoma (SCC; OR 0.6, 95% confidence interval 0.3–0.9). There was no significant gene-environment interaction of the variant *XRCC1* genotype and a history of therapeutic X-ray exposure. However, there was a statistically significant multiplicative interaction of *XRCC1* genotype and lifetime number of sunburns in SCC [likelihood ratio test (2 d.f.), $P < 0.02$]. Although the absolute risk of SCC associated with sunburns was similar across genotypes, the relative risk of SCC associated with painful sunburn history was significantly higher for homozygous variants than wild types (OR 6.8 for gln399gln and 1.5 for arg399arg). In summary, our data show that the homozygous *XRCC1* variant (gln399gln) is associated with a lower risk of non-melanoma skin cancer and suggest that the etiology of sunburn-related SCC may be significantly different by *XRCC1* genotype. These data, using the classic skin carcinogenesis model, provide new insight on the role of the *XRCC1* 399 polymorphism in neoplasia and may help explain the conflicting results relating this polymorphism to cancer risk at various sites.

INTRODUCTION

The incidence of NMSC[3] among United States Caucasians continues to increase at an accelerated rate. In New Hampshire, during the period 1979–1993, the incidence rate for BCC increased 80%, and the measured rate of increase for SCC was >230% (1). These trends indicate that NMSC is a burgeoning public health problem, and it is clear that a better understanding of the underlying mechanisms of carcinogenesis and individual susceptibility to this disease are needed.

NMSC is primarily a disease of UV radiation exposure. However, other exposures, such as ionizing radiation (2, 3) and arsenic (4, 5), can contribute to skin carcinogenesis (reviewed in Ref. 6). Host susceptibility factors are also clearly associated with NMSC, particularly pigmentation and the tendency to burn (7, 8). In addition, constitutional variation in DNA repair capacity has been associated with skin cancer occurrence (9). However, the precise genetic factors that contribute to this reduced repair phenotype have not been elucidated.

Recent studies have demonstrated that a polymorphism in the DNA base excision repair gene *XRCC1* (arg399gln) is associated with measurably reduced DNA repair capacity as assessed by the persistence of DNA adducts (10, 11), increased RBC Glycophorin A mutations (10), elevated sister chromatid exchanges (11, 12), and prolonged cell cycle delay (13). In addition, this same polymorphism has been reported to be associated with the occurrence of six solid tumors: head and neck cancer (14, 15),[4,5] breast cancer (16), lung cancer (17), bladder cancer (18), stomach cancer (19), and colorectal cancer (20). However, these data do not point to a consistent role of the XRCC1 gln399gln protein, as the genotype confers increased risk in some studies (14, 15–17, 19, 20) and a protective effect in others (18),[4,5] whereas three other reports have indicated no cancer association (21–23).

XRCC1 directly participates in both base excision and single-strand break repair (24, 25). The arg399gln polymorphism occurs at a conserved residue in the poly(ADP-ribose) polymerase binding domain of XRCC1 (26) and may alter the efficiency of repair processes. Although base excision repair does not directly repair UV photolesions, it is likely an important repair pathway for oxidative damage induced by either UV (27) or ionizing radiation exposure (28). Therefore, we have examined the *XRCC1* arg399gln polymorphism in a population-based case-control study of NMSC in New Hampshire.

STUDY POPULATION AND METHODS

Study Population. All newly diagnosed cases of BCC and SCC in New Hampshire were identified using an incident survey (1). A collaborative network of dermatologists and pathology laboratories in the state and bordering areas was established, and this allowed research personnel to identify new NMSC cases through active surveillance of these facilities. Study staff documented diagnosis date, tumor histology, anatomical site, and prior history of NMSCs from patient records. Cases for the case-control study were identified from the incident survey (diagnostic dates 7/1/1993 to 6/30/1995). Following physician consent and with the approval of the Dartmouth College Committee for the Protection of Human Subjects, patients were asked to voluntarily participate in the study (82% of contacted cases participated). Controls, derived from the New Hampshire Department of Transportation and the Healthcare Financing Administration enrollment lists, were frequency matched to cases on gender and age (69% of contacted controls participated). For both cases and controls, an in-home interview was conducted to gather information on sun-exposure histories and other demographic and lifestyle information. Interviewers also collected tap water samples and clipped toenail specimens and conducted a blood draw (86% of participants provided a blood specimen).

***XRCC1* Genotyping.** DNA was extracted from peripheral circulating blood specimens taken at the time of interview using Qiagen genomic DNA extraction kits. Genotyping of the *XRCC1* arg399gln polymorphism was done using a PCR-RFLP method. A 171-bp fragment was amplified using the following primer pair: 5′-CCAAGTACAGCCAGGTCCTA and 5′-AGTCT-

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[3] The abbreviations used are: NMSC, non-melanoma skin cancer; BCC, basal cell carcinoma; SCC, squamous cell cancer; CI, confidence interval; OR, odds ratio.

[4] A. Olshan, M. A. Watshon, M. C. Weissler, and D. A. Bell. XRCC1 polymorphisms and head and neck cancer, submitted for publication.

[5] E. Peters, N. E. Mueller, M. Posner, and K. T. Kelsey. The Arg/Gln XRCC1 DNA repair gene polymorphism and head and neck cancer, submitted for publication.

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Table 1 *Comparison of cases and controls by demographic traits and risk factors*

	Control (%)	BCC (%)	SCC (%)
Gender			
Male	263 (61.0)	281 (56.3)	164 (66.7)
Female	168 (39.0)	218 (43.7)	82 (33.3)
χ^2 *P*		<0.2	<0.2
Age			
≤50	80 (18.6)	131 (26.3)	15 (6.1)
51–60	80 (18.6)	100 (20.0)	38 (15.5)
61–70	191 (44.3)	180 (36.1)	121 (49.2)
>70	80 (18.6)	88 (17.6)	72 (29.3)
χ^2 *P*		<0.02	<0.001
Skin type[a]			
Tans	290 (67.6)	298 (59.7)	134 (54.5)
Burns	139 (32.4)	201 (40.3)	112 (45.5)
χ^2 *P*		<0.01	<0.001
Radiation therapy[b]			
No	397 (92.1)	433 (86.8)	215 (87.4)
Yes	34 (7.9)	66 (13.2)	31 (12.6)
χ^2 *P*		<0.01	<0.05
Lifetime painful sunburns[c]			
0–2	262 (61.6)	233 (47.2)	113 (46.3)
≥3	164 (38.4)	261 (52.8)	131 (53.7)
χ^2 *P*		<0.001	<0.001

[a] Tendency to tan or burn after initial sun exposure, missing data for two.
[b] IR for NMSC was excluded, $n = 13$.
[c] Number of lifetime painful sunburns; missing data for 12.

Table 2 *XRCC1 codon 399 genotype prevalence and association with NMSC*[a]

	Controls	BCC		SCC	
	n (%)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)
Codon 399					
Arg/arg	175 (40.6)	213 (42.7)	Ref	108 (43.9)	Ref
Arg/gln	185 (42.9)	227 (45.5)	1.0 (0.7–1.3)	113 (45.9)	1.0 (0.7–1.4)
Gln/gln	71 (16.5)	59 (11.8)	0.7 (0.4–1.0)	25 (10.2)	0.6 (0.3–0.9)

[a] ORs adjusted for age, sex, and tendency to burn.

GACTCCCCTCCGGAT. After a 4-min incubation at 94°C, 35 cycles of PCR were performed (94°C 30 s → 58°C 30 s → 72°C 30 s), followed by a 10-min extension at 72°C. The PCR product was then incubated with *Msp*I endonuclease at 37°C overnight. The polymorphism of interest disrupts an *Msp*I consensus sequence, rendering it resistant to digestion. Wild-type alleles were digested to 92, 61, and 18 bp (the 18-bp fragment results from a nonpolymorphic *Msp*I site that served as an internal control for complete enzymatic digestion). Positive and negative controls also were included in each determinate of genotype.

Statistical Methods. Crude and adjusted ORs and 95% CIs for the association of *XRCC1* genotype and case status were calculated using unconditional logistic regression (29). All adjusted models included age, sex, and tendency to sunburn (always burn, burn then tan, or always tan). Other confounders considered included cumulative sun hours as well as hair and eye color. Two primary exposures were considered: sunburn history and therapeutic ionizing radiation. Painful sunburns were assessed by questionnaire as the number of sunburns that were painful for ≥2 days; this variable was then dichotomized according to the median in controls (≥3 sunburns). Self report of ionizing radiation therapy was verified through medical records in 44 of 56 (79%) subjects. Ionizing radiation treatments for NMSC were not included in the analysis.

Interaction was explored multiple ways. We conducted a conventional test of interaction, a Log-likelihood test comparing a "full" model that contains both the main effects of genotypes and environment plus an (gene × environment) interaction term and a "reduced" model that does not contain the cross-product variable. The "joint" effects of gene and environment were examined using those with both low exposure and the arg399arg genotype as the referent group (30). Using the β estimates from this joint regression model, we assessed the relative excess risk from exposure within genotype strata. This was accomplished using proc LINCOM statements in STATA.

RESULTS

From the larger case-control study of NMSC, 1436 participants were interviewed, and 1176 individuals were studied. Those excluded either refused a blood draw ($n = 193$), had inconclusive results for *XRCC1* genotype ($n = 40$), or were non-Caucasians ($n = 27$). We restricted the analysis to Caucasians given the potential for significant ethnic variation in the *XRCC1* polymorphism (16, 17, 19). Those who were not included in the analysis did not significantly differ from those included, except for age; those excluded were significantly younger (data not shown). In sum, 499 BCC cases, 246 SCC cases, and 431 controls were analyzed.

BCC cases tended to be younger and SCC cases older than controls (Table 1). In addition, both case groups were significantly more likely to burn rather than tan after their first sun exposure of the season. As reported previously, case status was associated with a history of therapeutic ionizing radiation (2). A history of painful sunburns was also significantly more prevalent in cases than controls (Table 1).

Among controls, the variant 399gln allele frequency was 0.38, and the polymorphism was in Hardy-Weinberg equilibrium ($\chi^2 = 3.4$, $P = 0.07$). There were no significant associations of *XRCC1* genotype and demographic variables (data not shown). The prevalence of the homozygous variant gln399gln genotype was 16.5% (72 of 432) in controls, 11.8% (59 of 499) in BCC cases, and 10.2% (25 of 246) in SCC cases (Table 2). The adjusted OR (95% CI) for the gln399gln genotype in BCC was 0.7 (0.4–1.0), and 0.6 (0.3–0.9) in SCC. The point estimates for those with the heterozygote genotype were similar to the wild-type referent group for both BCC (OR 1.0, 95% CI 0.7–1.3) and SCC (OR 1.0, 95% CI 0.7–1.4). Adjustment for cumulative sun exposure and hair/eye color did not alter these point estimates.

Next, we explored interactions between *XRCC1* genotype and two established risk factors for NMSC: therapeutic ionizing radiation and number of lifetime painful sunburns. We compared the Log-likelihood scores of the logistic models with and without an interaction term, keeping genotype as a three-level variable (tests were done with 2 d.f.). For ionizing radiation, there was no evidence of interaction with either BCC ($P < 0.8$) or SCC ($P < 1.0$). There was limited evidence of interaction for sunburns and BCC ($P < 0.2$); however, the difference in models with and without the sunburn interaction terms was statistically significant for SCC ($P < 0.02$).

Additional analysis of interaction involved construction of a "joint model" of sunburn and *XRCC1* genotype (Table 3). The referent group was set as those with zero to two painful sunburns and the arg/arg genotype (according to our *a priori* hypothesis). For both BCC and SCC, the gln/gln genotype, in the absence of multiple sunburns, was associated with significantly reduced risk [BCC OR = 0.5 (95% CI 0.3–0.9), SCC OR = 0.3 (95% CI 0.1–0.6)]. Three or more sunburns were associated with increased risk, irrespective of *XRCC1* genotype. Finally, we assessed the relative risk from sunburn within genotype strata using the β estimates from the joint model (Table 4).

Table 3 *Regression model for the joint effects of XRCC1 genotype and sunburn*[a]

Lifetime sunburns	*XRCC1* genotype	β coefficient	OR (95% CI)
BCC			
0–2	Arg/arg		Ref
0–2	Arg/gln	−0.22	0.8 (0.6–1.2)
0–2	Gln/gln	−0.69	0.5 (0.3–0.9)
≥3	Arg/arg	0.21	1.2 (0.8–1.9)
≥3	Arg/gln	0.40	1.5 (1.0–2.3)
≥3	Gln/gln	0.25	1.3 (0.7–2.4)
SCC			
0–2	Arg/arg		Ref
0–2	Arg/gln	0.01	1.0 (0.6–1.6)
0–2	Gln/gln	−1.34	0.3 (0.1–0.6)
≥3	Arg/arg	0.40	1.5 (0.9–2.5)
≥3	Arg/gln	0.45	1.6 (0.9–2.6)
≥3	Gln/gln	0.57	1.8 (0.8–3.8)

[a] ORs adjusted for age, sex, and tendency to burn.

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Table 4 *Association of SCC and sunburn within XRCC1 genotype strata*[a]

	Wild type (arg/arg)	Heterozygote (arg/gln)	Variant (gln/gln)
Lifetime sunburns			
0–2	Ref	Ref	Ref
≥3	1.5 (0.9–2.5)	1.6 (0.9–2.6)	6.8 (2.4–19.2)

[a] ORs and CI are derived from the β coefficients of the joint effect model (given in Table 3).

Within wild-type (arg/arg) and heterozygous (arg/gln) strata, there was a modest risk of SCC with three or more painful sunburns (OR = 1.5 and 1.6, respectively). However, among those who were *XRCC1* gln399gln, the relative risk of SCC associated with a high number of sunburns was approximately seven compared with those having fewer than three sunburns [OR = 6.8 (95% CI 2.4–19.2)]. A case-only analysis of interaction was consistent with the model using controls [OR = 3.1 (95% CI 1.1–8.7)], indicating the observed interaction was not driven by population stratification in the controls.

DISCUSSION

Overall, in our population, the *XRCC1* gln399gln homozygote variant genotype was associated with a significantly reduced risk of NMSC. Our findings are seemingly at odds with both phenotypic studies (10, 11, 13) and many case-control studies (14, 15–17, 19, 20). However, whether the *399gln* allele is associated with increased or reduced cancer risk may be a function of selective pressures exerted on the cell, *e.g.*, if the variant protein has an altered repair efficiency, as suggested by phenotype studies, the resultant increased levels of damage might give rise to enhanced apoptosis at the time of cell division. If true, this would manifest as reduced risk for exposure-induced cancer. According to this model, the 399gln protein would be associated with reduced repair and increased cancer risk in both nondividing cells and apoptosis-abrogated cells but would be associated with reduced cancer risk in dividing cells that have the apoptotic mechanism intact.

This model is consistent with the results of our gene-environment analysis. Repeated sunburns may be viewed as the probability of having a field of p53 mutant cells [as suggested by the findings of Ouhtit *et al.* (31) and Einspahr *et al.* (32)], and p53 mutation abrogates keratinocyte apoptosis (33). In the absence of repeated sunburns, the gln399gln genotype is protective (apoptosis intact). Using the model described above, once the apoptotic mechanism is ablated (after multiple sunburns), the risk of skin cancer among the gln399gln should be markedly higher, reflecting the reduced repair phenotype, whereas the risk among those with arg alleles would not be dramatically altered. Our strata-specific ORs (arg399arg = 1.5 and gln399gln = 6.8) are strikingly consistent with this model.

There are, of course, other explanations for both our main gene effect and gene-environment interaction. These include possible linkage to another important polymorphism, differential effects of the polymorphism by carcinogen dose, and population stratification (although our case-case analysis suggests this is unlikely). Other groups have investigated this polymorphism for gene-environment interaction with conflicting findings. In a case-control study of breast cancer (16), the *XRCC1* polymorphism modified the effects of smoking and ionizing radiation such that the exposure-associated risks were highest among African-Americans with the arg399arg genotype. Stern *et al.* (18) suggested that heavy exposure might saturate the effects of the polymorphism; the 399gln genotype was associated with reduced bladder cancer risk but only among light smokers. Divine *et al.* (17) proposed that the penetrance of the 399gln genotype may be greater in those with high exposure. This possibility is also consistent with our data, as well as that of Sturgis *et al.* (14) and Stern *et al.* (18).

In sum, we have found that the main effect of the gln399gln genotype in skin cancer is risk reduction. Our findings of gene-environment interaction suggest two interpretations: (*a*) the absolute risk of SCC associated with sunburn is constant across genotypes; and (*b*) the relative risk associated with multiple sunburns is significantly elevated among gln399gln individuals, while being only modestly elevated among those with the 399arg allele. We have posited a model of the *XRCC1* polymorphism that may explain the inconsistent findings across studies. For each tumor type, the biological pathway responsible for the induction of apoptosis and the inactivation of this mechanism may impact both the ability to detect as well as the direction of the *XRCC1*-disease association. Furthermore, if the polymorphism functions differentially under conditions of "high" and "low" exposure, it will require significant numbers of cases in each exposure group to detect the differential effects of the *XRCC1* polymorphism. Finally, this likely will vary significantly not only by carcinogen exposure but also by disease, ethnicity, and geography. Additional *in vitro* and large population-based studies are needed to test this model, both in skin cancer as well as other exposure-induced cancers.

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