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Polymorphisms in DNA repair genes XRCC1 and XRCC3, occupational exposure to arsenic and sunlight, and the risk of non-melanoma skin cancer in a European case-control study ☆

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ABSTRACT

X-ray repair cross-complementing group 1 (*XRCC1*) and group 3 (*XRCC3*) polymorphisms are relatively frequent in Caucasian populations and may have implications in skin cancer modulation. A few studies have evaluated their association with non-melanoma skin cancer (NMSC), but the results are inconsistent. In the current study, we aim to assess the impact of *XRCC1* R399Q and *XRCC3* T241M polymorphisms on the risk of NMSC associated with sunlight and arsenic exposure. Study participants consist of 618 new cases of NMSC and 527 hospital-based controls frequency matched on age, sex, and county of residence from Hungary, Romania, and Slovakia. Adjusted effects are estimated using multivariable logistic regression. The results indicate an increased risk of squamous cell carcinoma (SCC) for the homozygous variant genotype of *XRCC1* R399Q (OR 2.53, 95% CI 1.14–5.65) and a protective effect against basal cell carcinoma (BCC) for the homozygous variant genotype of *XRCC3* T241M (OR 0.61, 95% CI 0.41–0.92), compared with the respective homozygous common genotypes. Significant interactions are detected between *XRCC3* T241M and sunlight exposure at work, and between *XRCC3* T241M and exposure to arsenic in drinking water (p-value for interaction <0.10). In conclusion, the current study demonstrates that polymorphisms in *XRCC* genes may modify the associations between skin cancer risk and exposure to sunlight or arsenic. Given the high prevalence of genetic polymorphisms modifying the association between exposure to environmental carcinogens and NMSC, these results are of substantial relevance to public health.

1. Introduction

Assessment of the synergistic effects of multiple environmental exposures and genetic polymorphisms in the causes of skin cancer is of great importance for understanding and evaluating human

Abbreviations: BCC, basal cell carcinoma; NMSC, non-melanoma skin cancer; SCC, squamous cell carcinoma; UVR, ultraviolet radiation; XRCC1, X-ray repair cross-complementing group 1; XRCC3, X-ray repair cross-complementing group 3

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health risks. However, in spite of extensive research and knowledge gained on non-melanoma skin cancer (NMSC) in recent years, there is little information about the role played by genes or gene-environment interactions in the genesis and development of the main histological subtypes, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).

The NMSC risk is associated with environmental and occupational risk factors, including sunlight and chemicals such as inorganic arsenic (IARC, 2004, 2012a, 2012b). Inorganic arsenic exposure occurs in a variety of workplaces for instance copper, lead, and zinc smelters, production and use of pesticides and wood preservatives, and glass manufacture (ATSDR, 2007). Inorganic arsenic is also found in drinking water in many regions of the world, mainly due to dissolution of arsenic-containing minerals to surrounding aquifers. Highly varying arsenic concentrations are found in parts of Asia, South America, North America and Central Europe (Smedley and Kinniburgh, 2002). A large number of people, particularly outdoor workers in construction, agriculture, horticulture, and forestry occupations are exposed to sunlight at the workplace, and often also in their ambient environment (IARC, 2002; Vecchia et al., 2007). The skin carcinogenicity of both arsenic and ultraviolet (UV) radiation may be modified by genetic polymorphisms or other host factors, such as skin pigmentation and sensitivity to UV exposure (Gallagher and Lee, 2006; Rossman, 2003).

Single Nucleotide Polymorphisms (SNPs) are naturally occurring variations in human DNA sequences and have been used to identify individual differences in susceptibility to various diseases, including skin cancer associated with environmental exposures (Berwick and Vineis, 2000; Houlston and Peto, 2004). Individuals with impaired DNA repair capability are at an increased risk for accumulating genetic alterations that could lead to mutagenic transformation and the development of skin cancer. In the past decade, a large number of epidemiological studies addressed associations between DNA repair genetic polymorphisms, including X-ray repair cross-complementing group 1 (*XRCC1*) and group 3 (*XRCC3*), and susceptibility to cancer. More than 40 studies investigated the *XRCC1* R399Q polymorphism and over 50 studies focused on the *XRCC3* T241M polymorphism, yet the findings are contradictory. Results from systematic reviews and meta-analyses of these DNA repair gene polymorphisms indicated associations with breast, lung, bladder, stomach, cervix, and head and neck cancers (Dong et al., 2008; Goode et al., 2002; Han et al., 2006; Vineis et al., 2009). Two other meta-analyses reported no significant association for internal cancers (Hu et al., 2005; Manuguerra et al., 2006). In recent meta-analyses, decreased risks for BCC were reported in association with *XRCC3* T241M (Dong et al., 2008; Han et al., 2006); however no skin cancer effects were reported for *XRCC1* R399Q or *XRCC3* T241M in others (Manuguerra et al., 2006; Vineis et al., 2009; Zhang et al., 2011). Some studies (summarized in Supplemental information Table 1, available online) reported negative associations for NMSC with the homozygous variant genotype of *XRCC1* R399Q (Han et al., 2004; Nelson et al., 2002) and both variant genotypes of *XRCC3* T241M (Han, 2004), positive associations with the heterozygous genotype of *XRCC1* R399Q (Kang et al., 2007) and *XRCC3* T241M (Jacobsen et al., 2003), and one study reported no associations with *XRCC1* R399Q and *XRCC3* T241M polymorphisms (Festa et al., 2005). An earlier study conducted on the same study population as in the current work identified a protective effect against BCC in carriers of the *XRCC3* T241M variant allele, but no association was identified for BCC and *XRCC1* R399Q (Thirumaran et al., 2006). The interaction between these genetic polymorphisms and sunlight exposure on NMSC risk was explored in three studies (Han et al., 2004; Nelson et al., 2002; Thirumaran et al., 2006); two studies detected a significant interaction between *XRCC1* R399 and lifetime sunburns as a proxy indicator of exposure on the risk of SCC (Han et al., 2004; Nelson et al., 2002). Although genome-wide association studies have identified genes associated with pigmentation, sun sensitivity and BCC risk, results have not been reported for *XRCC1* R399Q and *XRCC3* T241M (Gerstenblith et al., 2010; Zhang, 2012). To our knowledge there is no data available on the modification of skin cancer risk by these DNA repair genetic polymorphisms in association with arsenic and sunlight exposure at work, or arsenic exposure *via* drinking water. Clearly, additional investigation is needed, particularly on gene-environment interactions.

The present study focuses on effects for the *XRCC1* R399Q and *XRCC3* T241M polymorphisms on NMSC risk associated with lifetime exposure to arsenic and sunlight at the workplace, and arsenic exposure through consumption of contaminated water. We selected these DNA repair genetic polymorphisms because they occur frequently in Caucasian populations, and a number of studies suggest potential implications in cancer risk. However, a majority of published findings are related to cancers of the breast, lung, and bladder; only a few epidemiological studies evaluated the association between these polymorphisms and skin cancer, especially in the presence of environmental exposures, and these reported mixed results. The current study is based on the Arsenic Health Risk Assessment and Molecular Epidemiology – ASHRAM Study, a hospital-based case-control investigation of NMSC conducted among Caucasian populations in Central and Eastern Europe. Previous findings from this project indicated that the risk of NMSC increased with arsenic exposure from drinking water (Leonardi et al., 2012), increased, yet not statistically significant, with arsenic exposure at work (Surdu et al., 2013b) and decreased with occupational exposure to sunlight among light-skinned persons (Surdu et al., 2013a).

2. Material and methods

2.1. Study population

This study is based on a multinational European research project conducted in several regions of Hungary, Romania and Slovakia, between January 2003 and September 2004. The study population consisted of incident cases of skin, bladder and kidney cancers, and hospital-based controls. The study response rate was 81.6% among cases and 90% among controls; a detailed description of participant recruitment was published previously (Leonardi et al., 2012). The current study focuses on new cases of NMSC (International Classification of Disease – 10th Revision codes C44), aged 30–79 years, and having resided for at least one year in the study regions (*i.e.*, four counties of Hungary, two counties of Romania, and two counties of Slovakia). NMSC cases were identified by county hospitals pathologists who confirm skin cancers treated in all outpatient and inpatient health care settings (*e.g.*, physician offices and hospitals) located in the study area. Controls were defined as county hospital patients diagnosed during the study period with general surgical diseases (*i.e.*, appendicitis, abdominal hernia, duodenal ulcer, and cholelithiasis) or orthopedics and traumatology conditions (*i.e.*, fracture). Control subjects residing in the study area for at least one year were frequency matched to cases by county of residence, sex, and five year age group. Written informed consent was obtained from all cases and controls enrolled in the study. The study was reviewed and approved by ethical committees of hospitals involved in data collection and by the Institutional Review Board of the University at Albany, State University of New York, United States.

2.2. Exposure assessment

Local investigators conducted a face-to-face interview within 3 months of study enrollment. A questionnaire was used to collect information on demographics, socioeconomic indicators, family history of cancer, phenotypic characteristics such as skin pigmentation and sensitivity to sunburns, and lifestyle factors such as smoking and leisure sun exposure. The questionnaire also addressed residential and occupational histories related to drinking water sources and carcinogenic occupational risk factors.

An occupational exposure evaluation was based on expert assessment of lifetime work history, including job titles held for 1+years, job tasks, period working in each job, and industry. A participant was estimated as being exposed to

arsenic in dust/fumes or UV radiation if he or she had worked prior to the study diagnosis in a job which involved potential exposure. An in depth description of the occupational exposure ascertainment and findings are provided elsewhere (Surdu et al., 2013a, 2013b).

Detailed information regarding assessment of inorganic arsenic exposure through drinking water has been reported (Hough et al., 2010). In brief, exposure assessment was based on measurements in water samples collected from current and previous study area residences identified by the study questionnaire. Historical water-quality data collected by municipalities was used in exposure models. Total inorganic arsenic was measured by atomic absorption spectrometry with hydride generation (Lindberg et al., 2006). A chronic exposure index of arsenic in drinking water was constructed as a lifetime time-weighted average concentration for each subject.

2.3. Genotyping

Polymorphisms in DNA repair genes were selected for study based on the potential for individual variation and a high frequency of the variant allele (*i.e.*, $>20\%$). We consider polymorphisms in the *XRCC1* gene located at codon 399 and the *XRCC3* gene located at codon 241. Blood samples from cancer cases and controls recruited in Hungary, Romania and Slovakia were stored at $-80\,^{\circ}C$, until DNA isolation using Qiagen genomic DNA extraction kits (Qiagen GmbH, Hilden, Germany); a strict quality control/quality assurance procedure was followed. The TaqMan 5′ nuclease allelic discrimination assay (Applied Biosystems, Foster City, CA, USA) was employed for genotyping using a polymerase chain reaction platform, as previously described in detail (Thirumaran et al., 2006). Random verification of genotyping results from allelic discrimination assays by direct DNA sequencing showed $>99\%$ agreement for all assays. Control group polymorphism genotypes were distributed according to Hardy–Weinberg equilibrium (Rodriguez et al., 2009).

2.4. Statistical analysis

Frequency distributions of demographic characteristics and exposures were compared by case status in bivariate analyses. Bivariate analysis was also employed to investigate potential confounders and to assess correlations between covariates. Multivariable unconditional logistic regressions were conducted to calculate odds ratios (OR) and 95% confidence intervals (95% CI) for total NMSC, and separately for BCC and SCC. Odds ratios for main effects and interaction estimates were adjusted for skin complexion, family history of cancer, and exposure to arsenic in drinking water. Matching in case-control design shifts the exposure distribution among controls, introducing a selection bias contingent on associations with the matching factor; this requires adjustment during multivariable analysis. Our approach has the further benefit of preventing residual confounding by matching variables. To minimize the potential selection bias, we included the matching variables county of residence (categorical variable, eight counties) as well as sex (binary variable) and age (categorical variable, quartile groups) in all unconditional logistic models.

The joint effects of investigated gene repair polymorphisms and work-related exposure to arsenic and sunlight as well as exposure to arsenic in drinking water were estimated by including two-way interaction terms (*i.e.*, genotype*exposure) in the logistic regressions and testing for significance according to the Wald Test. Work-related exposures were defined as "ever" *vs.* "never". The environmental arsenic exposure, defined as average lifetime concentration in the residential water supplies, was dichotomized as "above" *vs.* "below" 16.7 μg/L (the 75th percentile of the control group distribution), level above which skin cancer risk increased in our earlier work (Leonardi et al., 2012). To facilitate the interaction analysis, homozygous variant *XRCC1* R399Q and *XRCC3* T241M genotypes were combined with heterozygous genotypes, and homozygous common genotypes were used for referent groups.

All analyses were conducted in SAS 9.2 software (SAS Institute, Cary, NC, USA). The main effect estimates were considered statistically significant if the two-tailed *p*-value was smaller than 0.05. Interaction effects were reported for two-tailed *p*-value smaller than 0.10.

3. Results

In unadjusted comparisons, NMSC cases ($n=618$) were slightly older than controls ($n=527$), reported less smoking, and had a higher propensity to light skin complexion and family history of cancer (Table 1). Cases also had lower arsenic exposure *via* drinking water and a higher prevalence of arsenic and sunlight exposure at work.

Genotype and allele frequencies of *XRCC1* R399Q and *XRCC3* T241M polymorphisms and their adjusted main effects on NMSC are presented in Table 2. The distribution of variant A allele in the *XRCC1* R399Q polymorphism was 36% for controls and 37% for NMSC (36% for BCC and 45% for SCC). A significantly increased adjusted odds ratio of SCC was found for the homozygous variant compared with the homozygous common genotype (OR 2.29, 95% CI 1.01–5.15). An increased, however not significant odds ratio was observed for SCC in subjects with the heterozygous genotype. No significant association with NMSC or BCC was detected for carriers of the heterozygous or the homozygous variant *XRCC1* R399Q polymorphism genotypes. The distribution of the variant T allele in the *XRCC3* T241M polymorphism was 41% for controls and 35% for NMSC (35% for BCC and 37% for SCC). Carriers of the variant T allele (heterozygous and homozygous variants) in the *XRCC3* T241M polymorphism had a lower risk of NMSC, mainly BCC, compared with homozygous common genotype carriers (BCC: OR 0.73, 95% CI 0.55–0.97 for the heterozygous genotype, OR 0.63, 95% CI 0.42–0.95 for the homozygous variant). The risk of SCC was modestly, yet non-significantly lower among carriers of the variant T allele.

Adjusted estimates for the joint effects of arsenic exposure at work, sunlight exposure at work, and exposure to arsenic *via* drinking water, with *XRCC1* R399Q polymorphism on NMSC risk are shown in Table 3. There was no evidence of interaction effects between the investigated genetic repair polymorphism and any exposure.

Adjusted joint effect results for the *XRCC3* T241M polymorphism with occupational and environmental co-exposures indicate no interaction with arsenic exposure at work (Table 4). However, our findings suggest an interaction between the effect of the *XRCC3* T241M polymorphism and the effect of work-related sunlight exposure on NMSC risk ($p<0.10$). Occupational exposure to sunlight had a protective effect against NMSC (OR 0.30, 95% CI 0.15–0.61) and BCC (OR 0.31, 95% CI 0.15–0.65), predominantly for the homozygous common genotype compared to the homozygous common genotype not exposed. An interaction was also detected between the *XRCC3* T241M polymorphism and drinking water arsenic exposure for NMSC ($p<0.10$), and particularly for SCC ($p<0.05$). The homozygous common genotype with higher exposure to arsenic in drinking water was associated with significantly elevated odds ratios for NMSC (OR 2.92, 95% CI 1.66–5.13) and SCC (OR 6.02, 95% CI 1.80–20.09) compared with the homozygous common genotype with lower exposure. In our study, county of residence was a strong predictor of arsenic exposure in drinking water ($p<0.0001$), and thus adjusted odds ratios were substantially different from the unadjusted; associations were not significant for sex and age.

4. Discussion

In this study, variant allele genotypes were significantly associated with skin cancer incidence. An increased risk of SCC was detected for the presence of the A allele in the *XRCC1* R399Q genetic polymorphism, and protective effects against total NMSC and BCC were detected for the T allele in the *XRCC3* T241M genetic polymorphism. We found evidence of interactions between the *XRCC3* T241M gene polymorphism with sunlight exposure at work, and with arsenic exposure in drinking water. The *XRCC1* R399Q gene polymorphism also influenced skin cancer risk among participants exposed to these carcinogens, but no interactions with arsenic or sunlight were detected. The investigation of gene-environment interactions are important in studying the impact of repair genes on skin cancers, since the effects of genetic polymorphisms may be apparent only in the presence of carcinogenic agents such as arsenic or sunlight. The investigated interactions are biologically plausible as the *XRCC1* gene plays an important role in the DNA base excision repair pathway, while the *XRCC3* gene is involved in the DNA homologous recombination repair

Table 1
Selected characteristics and exposures among study participants by non-melanoma skin cancer (NMSC) status.

Characteristics	Controls		Cases	
	n[a]	%, mean (median)	*n*[a]	%, mean (median)
Sex				
Female	255	48.4	333	53.9
Male	272	51.6	285	46.1
Age at interview (years)[b]				
≤ 52	136	25.8	78	12.6
53–61	131	24.9	119	19.3
62–70	144	27.3	183	29.6
≥ 71	116	22.0	238	38.5
Country				
Hungary	240	45.5	170	27.5
Romania	156	29.6	218	35.3
Slovakia	131	24.9	230	37.2
Education				
Years	524	10.1 (10.0)	616	9.9 (9.0)
Body Mass Index				
Weight (kg)/height (m^2)	526	22.9 (22.5)	613	22.1 (22.0)
Smoked > 100 cigarettes during lifetime				
No	276	52.4	392	63.4
Yes	251	47.6	226	36.6
Family history of cancer				
No	412	78.2	418	67.6
Yes	115	21.8	200	32.4
Skin pigmentation				
Medium/dark	310	58.9	312	50.6
Light	216	41.1	305	49.4
Arsenic exposure in drinking water (μg/L)[c]				
0–16.6	393	75.1	471	77.0
16.7–196.0	130	24.9	141	23.0
Arsenic exposure at work				
Never	445	84.4	471	76.2
Ever	82	15.6	147	23.8
Sunlight exposure at work				
Never	426	88.2	491	86.1
Ever	57	11.8	79	13.9

[a] Total number of subjects varies due to missing data for covariates.
[b] Quartiles of the control group distribution.
[c] Lifetime average concentration of arsenic in drinking water, the upper quartile of the control group distribution.

Table 2
Adjusted odds ratios between *XRCC1* and *XRCC3* gene polymorphisms and skin cancer (non-melanoma skin cancer, NMSC; basal cell carcinoma, BCC; squamous cell carcinoma, SCC).

Genetic polymorphisms	Controls	NMSC		BCC		SCC	
	n	*n*	OR[a] (95% CI)	*n*	OR[a] (95% CI)	*n*	OR[a] (95% CI)
***XRCC1* R399Q**							
GG	209	240	1.00 (referent)	209	1.00 (referent)	21	1.00 (referent)
GA	243	284	1.10 (0.84–1.44)	232	1.05 (0.79–1.40)	34	1.64 (0.87–3.10)
AA	63	84	1.26 (0.84–1.89)	65	1.09 (0.71–1.67)	14	2.29 (1.01–5.15)
Variant A allele frequency	0.36	0.37		0.36		0.45	
***XRCC3* T241M**							
CC	176	259	1.00 (referent)	216	1.00 (referent)	29	1.00 (referent)
CT	255	270	0.71 (0.54–0.93)	226	0.73 (0.55–0.97)	29	0.68 (0.37–1.25)
TT	84	79	0.64 (0.43–0.95)	64	0.63 (0.42–0.95)	11	0.80 (0.35–1.82)
Variant T allele frequency	0.41	0.35		0.35		0.37	

[a] Odds ratios (95% CI) adjusted for age, sex, county of residence, family history of cancer, skin pigmentation, arsenic exposure in drinking water.

pathway (Savas et al., 2004; Thompson and West, 2000; Vogel, 2006). Base excision repair is critical to restore single-strand DNA breaks, and nitrogenous base damage (Breton et al., 2007). The homologous recombination mechanism is involved in the repair of double-strand DNA breaks (Hartwig et al., 2003; Hughes et al., 2011; Ichihashi et al., 2003). Sunlight and arsenic carcinogenesis may act through several modes of action that are believed to involve the formation of reactive oxygen species. Reactive oxygen species can induce oxidative DNA damage including single-strand breaks, nitrogenous base damage, and double-strand breaks (Ghosh et al., 2008; Karagas et al., 2006; Tchounwou et al., 2003). Arsenic also inhibits DNA repair processes, mainly *via* damage to zinc-finger proteins, and possibly through altered gene expression secondary to changes in DNA methylation (Abernathy et al., 1999; Hughes, 2002; Martinez et al., 2011).

Findings from prior studies of NMSC and the *XRCC1* R399Q and *XRCC3* T241M polymorphisms are summarized in Supplemental information Table 1 (available online). The studies by Nelson et al. (2002) and Han et al. (2004) reported reduced risks of BCC and SCC in association with the *XRCC1* R399Q (OR 0.6, 95% CI 0.3–0.9;

Table 3
Joint effect between occupational/environmental exposures and *XRCC1* gene polymorphisms on skin cancer risk (non-melanoma skin cancer, NMSC; basal cell carcinoma, BCC; squamous cell carcinoma, SCC).

Exposures	*XRCC*1 polymorphism	Controls	NMSC		BCC		SCC	
		n	*n*	OR[a] (95% CI)	*n*	OR[a] (95% CI)	*n*	OR[a] (95% CI)
Arsenic at work	***XRCC1* R399Q**							
Never	GG	177	177	1.00 (referent)	159	1.00 (referent)	13	1.00 (referent)
	GA, AA	257	287	1.22 (0.91–1.62)	234	1.12 (0.83–1.51)	33	2.13 (1.04–4.37)
Ever	GG	32	63	1.43 (0.85–2.38)	50	1.32 (0.77–2.25)	8	2.15 (0.74–6.29)
	GA, AA	49	81	1.22 (0.78–1.90)	63	1.12 (0.70–1.79)	15	2.51 (1.00–6.27)
p-Value for interaction				0.286		0.422		0.359
Sunlight at work	***XRCC1* R399Q**							
Never	GG	168	185	1.00 (referent)	162	1.00 (referent)	16	1.00 (referent)
	GA, AA	246	298	1.19 (0.89–1.60)	243	1.12 (0.83–1.52)	37	1.76 (0.89–3.47)
Ever	GG	22	33	0.53 (0.26–1.09)	28	0.50 (0.24–1.05)	3	0.78 (0.15–4.02)
	GA, AA	35	45	0.46 (0.24–0.88)	35	0.41 (0.21–0.80)	6	0.97 (0.23–4.16)
p-Value for interaction				0.445		0.456		0.693
Arsenic in drinking water[b]	***XRCC1* R399Q**							
0–16.6	GG	157	180	1.00 (referent)	154	1.00 (referent)	16	1.00 (referent)
	GA, AA	230	289	1.21 (0.90–1.62)	232	1.13 (0.83–1.54)	37	1.85 (0.94–3.67)
16.7–196.0	GG	52	60	2.43 (1.43–4.12)	55	2.36 (1.38–4.04)	5	2.47 (0.71–8.66)
	GA, AA	76	79	2.24 (1.38–3.65)	65	2.04 (1.23–3.38)	11	4.01 (1.33–12.09)
p-Value for interaction				0.383		0.392		0.852

[a] Odds ratios (95% CI) adjusted for age, sex, county of residence, family history of cancer, skin pigmentation, arsenic exposure in drinking water.
[b] Lifetime average concentration of arsenic in drinking water (μg/L).

Table 4
Joint effect between occupational/environmental exposures and *XRCC3* gene polymorphisms on skin cancer risk (non-melanoma skin cancer, NMSC; basal cell carcinoma, BCC; squamous cell carcinoma, SCC).

Exposures	*XRCC*3 polymorphism	Controls	NMSC		BCC		SCC	
		n	*n*	OR[a] (95% CI)	*n*	OR[a] (95% CI)	*n*	OR[a] (95% CI)
Arsenic at work	***XRCC3* T241M**							
Never	CC	150	201	1.00 (referent)	172	1.00 (referent)	19	1.00 (referent)
	CT, TT	284	263	0.70 (0.52–0.94)	221	0.71 (0.53–0.96)	27	0.73 (0.38–1.43)
Ever	CC	26	58	1.20 (0.69–2.09)	44	1.18 (0.66–2.11)	10	1.53 (0.56–4.17)
	CT, TT	55	86	0.79 (0.51–1.23)	69	0.78 (0.49–1.24)	13	1.03 (0.42–2.54)
p-Value for interaction				0.859		0.832		0.896
Sunlight at work	***XRCC3* T241M**							
Never	CC	139	211	1.00 (referent)	176	1.00 (referent)	24	1.00 (referent)
	CT, TT	275	272	0.63 (0.47–0.85)	229	0.65 (0.48–0.89)	29	0.60 (0.31–1.14)
Ever	CC	24	31	0.30 (0.15–0.61)	27	0.31 (0.15–0.65)	2	0.24 (0.04–1.55)
	CT, TT	33	47	0.38 (0.20–0.72)	36	0.34 (0.18–0.67)	7	0.69 (0.17–2.80)
p-Value for interaction				0.089		0.217		0.102
Arsenic in drinking water[b]	***XRCC3* T241M**							
0–16.6	CC	137	194	1.00 (referent)	164	1.00 (referent)	18	1.00 (referent)
	CT, TT	250	275	0.79 (0.58–1.06)	222	0.77 (0.56–1.05)	35	1.07 (0.55–2.08)
16.7–196.0	CC	39	65	2.92 (1.66–5.13)	52	2.57 (1.44–4.60)	11	6.02 (1.80–20.09)
	CT, TT	89	74	1.33 (0.83–2.15)	68	1.36 (0.84–2.22)	5	1.12 (0.33–3.81)
p-Value for interaction				0.087		0.262		0.019

[a] Odds ratios (95% CI) adjusted for age, sex, county of residence, family history of cancer, skin pigmentation, arsenic exposure in drinking water.
[b] Lifetime average concentration of arsenic in drinking water (μg/L).

OR 0.61, 95% CI 0.39–0.97), respectively. Another study reported no association for *XRCC1* R399Q variant genotypes and BCC (Festa et al., 2005). Thirumaran et al. (2006) previously reported no effects for *XRCC1* R399Q on BCC in our study population. The earlier analysis did not investigate an association with SCC, and employed a different statistical approach from ours; whereas the previous study adjusted for age, sex, and nationality, we considered age, sex, county of residence, family history of cancer, skin pigmentation, and arsenic exposure in drinking water as potential confounders and thus the difference may reflect residual confounding, or possibly overadjustment contingent on the true underlying population relative risk. The number of participants in the prior analysis is also somewhat larger because our sample is restricted to participants with complete occupational exposure information. Similar to our study, Kang et al. (2007) reported increased risks of BCC and SCC in carriers of the heterozygous *XRCC1* R399Q genotype, with statistical significance for BCC (OR 2.78, 95% CI 1.30–5.92). Regarding the *XRCC3* T241M polymorphism, Jacobsen et al. (2003) detected an elevated risk for BCC (OR 1.46, 95% CI 1.04–2.05) in association with heterozygous *XRCC3* T241M genotype, and a decreased BCC risk among carriers of the homozygous variant genotype, although not of statistical significance. Significant protective effects for BCC (OR 0.67, 95% CI 0.49–0.91 for heterozygous; OR 0.57, 95% CI 0.35–0.93 for homozygous) similar to ours were observed by Han (2004) in carriers of variant genotypes, and for SCC (OR 0.69, 95% CI 0.51–0.94) in carriers of the homozygous variant. Festa et al. (2005) detected non-significant increased risks for BCC in association with *XRCC3* T241M variant genotypes. Thirumaran et al. (2006) previously reported protective effects for the *XRCC3* T241M variant genotypes

against BCC (OR 0.71, 95% CI 0.54–0.92 for heterozygous; OR 0.54, 95% CI 0.36–0.80 for homozygous).

The absence of clear associations between *XRCC1* R399Q variants and BCC in the present study might be due to compensatory effects from biological repair mechanisms. The protective effect we detected for variant allele genotypes on NMSC risk is not uncommon. This effect was previously reported not only for *XRCC3*, but also for other DNA repair genes; for example, Xeroderma pigmentosum complementation groups A (*XPA*) and D (*XPD*), which are involved in the nucleotide excision repair pathway (Applebaum et al., 2007; Han et al., 2005; Miller et al., 2006). Contradictory associations reported for the *XRCC3* T241M variant allele and different cancers may be explained by tissue-specific differences in the balance between repair pathways and apoptosis resulting in protective signal in some tissues and mutations in others (Bowen et al., 2003); for instance, reduced NMSC risk but increased risk of bladder and breast cancer.

Previous reports from the ASHRAM study showed increased, but non-significant risks of BCC and SCC among participants with workplace arsenic exposure (Surdu et al., 2013b). Sunlight exposure at work, on the other hand, was significantly associated with lower risks of BCC and SCC, mainly in subjects with light skin complexion (Surdu et al., 2013a). Although occupational epidemiological studies have shown associations between sunlight exposure and a reduced risk for various cancers including malignant lymphoma and renal carcinoma (Boffetta et al., 2008; Karami et al., 2010), our estimate of sunlight exposure at work might be confounded by some other unmeasured factor that reduced the risk; for example, fewer holidays with intense sunlight or socioeconomic characteristics. As the effect is modest, a chance finding cannot be ruled out. In the current study, we did not detect an interaction between *XRCC1* R399Q and *XRCC3* T241M polymorphisms and work-related arsenic exposure. Unfortunately, we were unable to evaluate heterogeneity of NMSC risk by workplace arsenic as nearly all occupational exposures were at low levels (*i.e.*, $n=3$ subjects assigned to high exposure probability and intensity for workplace arsenic). Our results also show no interaction between *XRCC1* R399Q and sunlight exposure at work, yet indicate that the *XRCC3* T241M gene polymorphism may interact with workplace sunlight exposure by reducing the NMSC risk among carriers of the homozygous common genotype. Again, the small number of participants with high sunlight exposure at work precluded an analysis of risk modification by exposure level. Only one previous study evaluated a potential effect of *XRCC1* R399Q polymorphism on skin cancer risk in relation to cumulative sunlight exposure, but from recreational exposure (Han et al., 2004). The authors reported lower risks for the homozygous variant genotype, and a significant increased SCC risk among carriers of the homozygous common genotype in association with high exposure; however, the risk variation across genotype-exposure categories was not statistically significant. Self-reported tendency to sunburn was also employed as a proxy for sunlight exposure, and an interaction with the *XRCC1* R399Q polymorphism on SCC risk was indicated in two studies (Han et al., 2004; Nelson et al., 2002), while no interaction with the *XRCC3* T241M polymorphism on BCC risk was reported (Thirumaran et al., 2006).

Another recent ASHRAM study reported a significantly elevated risk of BCC associated with the exposure to arsenic through drinking water (Leonardi et al., 2012). In the current study, we detected a joint effect between the *XRCC3* T241M genetic polymorphism and arsenic exposure through drinking water on skin cancer risk. Among participants chronically exposed to concentrations of arsenic in drinking water ≥ 16.7 μg/L, statistically significant 3-fold total NMSC and 6-fold SCC risk increases were associated with the homozygous common genotype compared to the referent group. These results underscore the importance of individual genetic susceptibility in modifying the skin cancer risk at moderate arsenic exposure levels. Furthermore, existing evidence implicates the inhibition of DNA repair as an important biologic mechanism for arsenic-induced effects experienced at lower levels of exposure (Hughes et al., 2011).

In the current study, control distributions of the variant *XRCC1* R399Q allele (36%) and the variant *XRCC1* R399Q allele (41%) were similar to frequencies reported in other Caucasian populations, ranging from 30% to 48% for *XRCC1* R399Q and from 30% to 41% for *XRCC3* T241M (Dong et al., 2008; Hu et al., 2005). More than one third of controls were carriers of the homozygous common allele for the *XRCC3* T241M gene polymorphism in our study, and we found that this polymorphism may modify skin cancer risk among participants with exposure to certain environmental carcinogens. Therefore, these results may be important for assessing risk, setting environmental standards, and developing public health policies that will adequately protect susceptible population groups.

This study is vulnerable to several limitations inherent to our hospital-based case-control design. The use of hospital controls may not represent the source population for that study from which cases originated, leading to a possible selection bias. To reduce the potential for such a bias, control participants were recruited from a larger list of hospitals in the study area than were cases, but including the hospitals used for case enrollment. A validation study conducted using census data showed that cases and controls had similar ascertainment by geographic area (Leonardi et al., 2012). A selection bias may also be of concern if the genetic repair polymorphisms examined, or the occupational and environmental exposures investigated, were associated with hospitalization for the diseases used to select of controls, but this is unlikely. However, to minimize the possibility for a selection bias, controls were recruited using diagnoses for which there was no prior evidence for links to the exposures considered. In addition, several different control diagnoses were employed which we expect to dilute any potential selection bias that may have been introduced by a specific control diagnosis.

Misclassification of genotype polymorphisms may introduce information bias in the study findings. Genotypes were identified by investigators unaware of case status. Consequently, any measurement error is expected to be non-differential and is likely to bias results towards the null hypothesis of no effect. The work-related exposure evaluation was based on experts' assessment of lifetime occupation histories and the experts were blinded to participant disease status. To minimize the possibility for information bias from exposure misclassification, local experts followed detailed coding guidelines, and participated in training workshops and validation exercises. In addition, the potential for participants' recall bias was minimized by using a validated questionnaire and conducting interviews with trained interviewers who followed a standardized protocol. Neither the participants nor the interviewers were aware of the present study hypothesis and therefore, any bias in the collection of occupation histories would not be different by case status. Exposure to arsenic *via* drinking water was estimated using lifetime water consumption patterns and arsenic concentration measurements from residential drinking water samples. Water samples were analyzed following strict quality assurance and quality control laboratory procedures. Potential exposure misclassifications are expected to be similar in cases and controls, and therefore, any bias due to random error is likely to be biased towards the null hypothesis of no effect.

We do not anticipate that cigarette smoking and seafood consumption, which are sources of arsenic exposure, vary by arsenic exposure in drinking water or at work. However, we investigated and found no confounding by smoking, while seafood is not an important part of the regional diet. In addition, we conducted

sensitivity analyses by excluding the participants who had the sum of arsenic metabolites in urine <2.5 μg/L (23% of participants), as this would indicate background arsenic exposure primarily from diet and smoking ($\sim$2–3 μg per day) (Lindberg et al., 2006). We detected similar, but less precise, point estimates due to the smaller number of participants analyzed. In addition, we employed a significance level of 0.10 to increase the probability of detecting interactions between genetic polymorphisms and environmental exposures; this strategy is commonly used to increase statistical power to detect heterogeneous effects. However, this liberal strategy increases the likelihood for a false positive result.

This study has several important strengths, including a high study response rate and a large sample size. When participation refusal rates are large, the interpretation of study results becomes increasingly difficult as the relation between NMSC and exposures of interest may be different for eligible participants and non-participants. This study had sufficient statistical power to detect relatively small associations, yet, the number of subjects per stratum became sparse for SCC during the interaction analysis. Consequently, the precision of interaction estimates for this histological subtype was limited. Another major strength of our study is the pathological confirmation of incident NMSC for approximately 94% of cases (the remaining 6% were confirmed by dermatologist consultation). A robust case definition (*e.g.*, biopsy histopathology) is critical, as the errant inclusion of case-diseases unrelated to the exposures of interest is likely to bias the study estimates toward to the null value of no effect. The results were reported by main histological types of NMSC, BCC and SCC. We furthermore were able to evaluate and adjust for confounding by several major factors of interest, using the detailed information collected during face-to-face interview, and employing a study questionnaire developed and piloted in the study area. Though interpretation of the reported results are somewhat limited by the observational nature of our study, our design offers many strengths and minimizes the possibility for bias.

5. Conclusion

The results of this study support previous findings showing associations between the *XRCC1* R399Q and *XRCC3* T241M gene polymorphisms and skin cancer. In addition, our study is the first to our knowledge to suggest that skin cancer development associated with sunlight and arsenic exposure may be modified by these DNA repair gene polymorphisms. Although the polymorphisms of DNA repair genes may cause only small alterations in cancer susceptibility, because they are relatively prevalent in the study population and have the potential to influence the risk of skin cancer, the associations we describe herein are likely to have significant public health implications.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2014.08.020.

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