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Single nucleotide polymorphisms in DNA repair genes and basal cell carcinoma of skin

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In addition to environmental exposures like UV radiation and, in some cases, arsenic contamination of drinking water, genetic factors may also influence the individual susceptibility to basal cell carcinoma of skin (BCC). In the present study, 529 cases diagnosed with BCC and 533 controls from Hungary, Romania and Slovakia were genotyped for one polymorphism in each of seven DNA repair genes. The variant allele for T241M (C>T) polymorphism in the *XRCC3* gene was associated with a decreased cancer risk [odds ratio (OR), 0.73; 95% confidence interval (CI), 0.61–0.88; $P = 0.0007$, multiple testing corrected $P = 0.004$]. The risk of multiple BCC was significantly lower among variant allele carriers than in non-carriers ($P = 0.04$). Men homozygous for the C-allele for E185Q (G>C) polymorphism in the *NBS1* gene showed an increased BCC risk (OR, 2.19; 95% CI, 1.23–3.91), but not women (OR, 0.84; 95% CI, 0.49–1.47). In men, the age and nationality adjusted OR for the genotype CC (*XRCC3*)/CC (*NBS1*) was 8.79 (95% CI, 2.10–36.8), compared with the genotype TT (*XRCC3*)/GG (*NBS1*). The data from this study show overall risk modulation of BCC by variant allele for T241M polymorphism in *XRCC3* and gender-specific effect by E185Q polymorphism in *NBS1*.

Introduction

Basal cell carcinoma (BCC) is the most common neoplasm of the skin and accounts for >75% of all skin cancers (1,2). BCC occurs mainly sporadically, but some rare genetic disorders, like Gorlin's syndrome and xeroderma pigmentosum, result in multiple tumors with an early onset (3). BCC tumors grow slowly and are only locally invasive; however, these cause extensive morbidity through recurrence and tissue destruction (4). The etiology of BCC involves an interplay between genetic and environmental factors, such as UV radiation that induces mutations in critical genes and provides growth advantage to the affected cells for clonal expansion (5,6). Arsenic ingestion through drinking water has also been associated with increased risk of non-melanoma skin cancers, including BCC (7).

The involvement of genetic factors in risk modulation may result in inter-individual differences in susceptibility to BCC. The removal of DNA photoproducts formed by UV exposure in different cells of the skin and the repair of consequential strand breaks require functional repair enzymes. Various studies have shown large inter-individual variation in DNA repair capacity, and individuals with low repair capacity are probably at an increased risk for different cancers including BCC (8–13). Many genes that encode enzymes involved in DNA repair carry non-synonymous single nucleotide polymorphisms (SNPs) with potential to modulate gene function (14). Association between variant alleles in different repair genes and modulation of risk of cancer, including various types of skin malignancies, has been reported (15–17). Two studies on BCC have found a risk modulation by different haplotype combinations in *XPD* and *XRCC3* genes (18,19). However, negative or ambiguous associations have been reported in other studies (20–22).

This report is based on BCC cases and controls recruited from areas of Hungary, Romania and Slovakia (23). Genotype data for non-synonymous SNPs in seven genes that encode enzymes involved in different DNA repair pathways were analyzed. The aim of the study was to determine the effect of selected genetic polymorphisms in the investigated DNA repair genes on the modulation of BCC risk and possible interaction with environmental and life-style factors.

Materials and methods

Study population

Cases and controls were recruited as part of a large study designed to evaluate the risk of various cancers due to environmental arsenic exposure in Hungary, Romania and Slovakia between 2002 and 2004. The recruitment was carried out in the counties of Bacs, Bekes, Csongrad and Jasz-Nagykun-Szolnok in Hungary; Bihor and Arad in Romania; and Banska Bytrica and Nitra in Slovakia. These areas, with universal health care services, were selected because of the low to moderate exposure of their population to arsenic in the last 20 years. The cases and controls selected were of Hungarian, Romanian and Slovak nationalities (23). Skin cancer patients were invited on the basis of histopathological examinations by pathologists. Skin types were classified on the basis of complexion and the effect of sun-exposure; the Fitzpatrick classification was not used for technical reasons. Hospital-based controls were included in the study, subject to fulfillment of a set of criteria. All general hospitals in the study areas were involved in the process of control recruitment. A rotation scheme was used in order to achieve appropriate geographical distribution. The controls were broadly matched with cases for age, gender, country of residence and ethnicity. Controls included general surgery, orthopedic and trauma patients aged 30–79 years with conditions like appendicitis, abdominal hernias,

Abbreviations: BCC, basal cell carcinoma; CI, confidence interval; OR, odds ratio; PCR, polymerase chain reaction; SNP, single nucleotide polymorphism.

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duodenal ulcers, cholelithiasis and fractures. Patients with malignant tumors, diabetes and cardiovascular diseases were excluded as controls.

Clinicians took venous blood and other biological samples from cases and controls after signing of consent forms. The blood samples were kept deep frozen at −80°C until analysis. Cases and controls recruited for the study were interviewed by trained personnel and they completed a general questionnaire, which included information on individual cumulative sun exposure in summer, sun-tanning, skin complexion, effects of sun exposure on skin and age/s at diagnosis of BCC. Ethnic background for cases and controls was recorded along with other characteristics of the study population. Local ethical boards approved the study plan and design.

Genotyping

DNA was isolated from blood samples from cases and controls using Qiagen mini-preparation kits and genotyped for seven different SNPs in DNA repair genes. The polymorphisms and genes investigated included the nucleotide excision repair genes *XPC* (A>C; K939Q), *XPD* (A>C; K751Q) and *XPG* (G>C; D1104H); base-excision repair genes *APEX1* (T>G; D148E) and *XRCC1* (G>A; R399Q); and double strand break repair genes *XRCC3* (C>T; T241M) and *NBS1* (G>C; E185Q). All the polymorphisms included in the study were non-synonymous and had minor allele frequencies >0.2 in order to achieve sufficient statistical power. Genotyping was performed by the 5′ nuclease allelic discrimination assay (TaqMan) in 96-well format. TaqMan primers and probes were purchased from Applied Biosystems under 'assay by design'. Primer and probe sequences used for genotyping are given in a Supplementary Table 1. Polymerase chain reaction (PCR) was performed in 5–10 µl volume reaction using 5 ng DNA as template, pre-made master mix and 0.5× probe-primer mix. The initial temperature conditions for PCR were set at 50°C for 2 min and 95°C for 10 min followed by 35–40 cycles at 92°C for 15 s and 60°C for 1 min. Genotyping on amplified PCR products was scored by differences in VIC and FAM fluorescent level in plate read operation on ABI PRISM 7900HT sequence detection system (Applied Biosystems, Foster City, CA) using SDS 1.2 software. Post-operation data were transferred as Microsoft Excel data and converted into genotype information. All genotypes were determined in completely blinded manner and the genotyping laboratory was not provided with information about case–control status.

Direct DNA sequencing

Eight percent of genotyping results from allelic discrimination assays were randomly verified by direct DNA sequencing. The sequencing reactions were performed using BigDye^R Terminator Cycle sequencing kit (Applied Biosystems) in a 10 µl volume containing PCR product pre-treated with ExoSapIT (Amersham Biosciences, Uppsala, Sweden) and a sequencing primer. The temperature conditions set for sequencing reactions were 96°C for 2 min followed by 27 cycles at 96°C for 30 s, 54°C for 10 s and 60°C for 4 min. Sequencing reaction products were precipitated with 2-propanol, washed with 75% ethanol, resuspended in 25 µl water and loaded onto ABI prism 3100 Genetic analyzer (Applied Biosystem). Primary sequencing data were analyzed using a sequence analysis program (Applied Biosystems).

Statistical analysis

The Hardy–Weinberg equilibrium in cases and controls was assessed using allele frequencies. Statistical significance of differences between observed and expected genotype frequencies was determined by Pearson's χ^2-test. Odds ratios (OR), 95% confidence intervals (CI) and *P*-values assessed the association of BCC and genotype, which were estimated using logistic regression adjusted for age of diagnosis of first BCC (as a continuous variable), gender and nationality. The analyses started with investigation of the effect of a specific factor on cancer incidence and results were summarized as *P*-values. Subsequently, OR and 95% CI were used to compare risk of BCC among different factor levels. Overall, no major difference was observed between OR calculated with and without adjustment (data not shown). *P*-values were corrected for multiple testing by the Westfall and Young permutation method (24). A test of trend was calculated by treating the three genotypes (major allele homozygous, heterozygous and variant allele homozygous) as ordinal variables (0, 1 and 2, respectively) for each polymorphism. The combined effect of *XRCC3* and *NBS1* genotypes was also determined. The observed differences between males and females in risk modulation motivated a gender-specific analysis of the data. The possible interaction of *XRCC3* polymorphisms, skin type and sun exposure was studied by multivariable logistic regression, where the genotype was modeled as a dichotomous variable (carriers and non-carriers), and age, gender, nationality, complexion and skin response to sun were treated as covariates. The effect of the *XRCC3* genotypes on the recurrence of BCC was assessed by logistic regression; the association of *XRCC3* with the age of onset of BCC was explored by Kruskal–Wallis tests. All statistical analyses were conducted using SAS version 9.1 software. Owing to inconsistency of the current data on the functional effects of the studied polymorphisms, all tests applied were two-sided.

Results

The distribution of cases and controls according to different variables is provided in Table I. The mean age of 529 cases (237 men and 292 women) at the time of diagnosis was 63.5 (±11.7) years (median 66; range 2–85) and the mean age of 533 controls (274 men and 259 women) was 60.0 (±11.8) years (median 61; range 28–82). Seventy-nine cases (38 men and 41 women) presented with multiple BCC. The average cumulative sun exposure did not show a statistically significant association with BCC risk. Skin complexion and effect of sun on skin were significantly associated with BCC (Table I).

Random verification of allelic discrimination assay results by direct DNA sequencing showed complete concordance of data from the two methods. Genotype distributions for all polymorphisms in both cases and controls were in accordance with the Hardy–Weinberg distribution. The frequencies of variant alleles for the different polymorphisms were in accordance with earlier reports from European populations (25,26).

No significant differences were found in the genotype distributions of *XPC*, *XPD*, *XPG*, *XRCC1* or *APEX1* between BCC cases and controls (Table II). Carriers of the variant T-allele for T241M (C>T) polymorphism in the *XRCC3* gene showed a statistically significant decreased risk of BCC (OR, 0.66; 95% CI, 0.51–0.86; $P = 0.002$; *P*-value adjusted for multiple testing, 0.01; results not shown). The *P*-value associated with the trend test was 0.0009. The T-allele for T241M (C>T) polymorphism in the *XRCC*3 gene was associated with decreased risk (OR, 0.73; 95% CI, 0.61–0.88; $P = 0.0007$; multiple testing corrected $P = 0.004$). After adjustment for age, gender, nationality, complexion and sun-effect on skin, the estimated OR were 0.73 (95% CI, 0.55–0.96) for heterozygotes and 0.56 (95% CI, 0.38–0.84) for variant allele homozygotes. The frequency of variant allele carriers for T241M *XRCC3* polymorphism was also lower in cases with multiple BCC than in controls ($P = 0.04$); the estimated OR for multiple BCC adjusted for age, gender and nationality were 0.63 (95% CI, 0.37–1.06) for heterozygotes and 0.46 (95% CI, 0.19– 1.11) for homozygotes with multiple BCC, compared with wild-type genotypes (results not shown).

The gender-specific analysis of the data showed protective effect of the variant T-allele in the *XRCC3* gene in both men and women (Table II). The interaction between gender and *XRCC3* genotype was not significant. The data also showed an association of variant allele for the E185Q polymorphism in the *NBS1* gene with increased risk of BCC in men (OR, 1.44; 95% CI, 1.10–1.88; $P = 0.008$), but not for women (OR, 0.96; 95% CI, 0.74–1.24; $P = 0.76$). In men (though not women) there was evidence of interaction between *XRCC3* and *NBS1* genotypes with the highest risk among homozygotes; the age and nationality adjusted OR for the genotype CC (*XRCC3*)/ CC (*NBS1*) was 8.79 (95% CI, 2.37–40.38; Figure 1), compared with the genotype TT (*XRCC3*)/GG (*NBS1*). No other genotype combination showed a statistically significant effect (data not shown).

The proportion of BCC patients affected by second malignancies was lower for the carriers of the variant T-allele in the *XRCC3* gene than for common allele homozygotes (Table III).

Table I. Distribution of cases and controls for different variables, and estimated ORs

Variable	Cases (with BCC)		Controls		OR	95% CI		*P*-value*
	No.	%	No.	%				
Complexion								
Light	280	53	212	40	1	–	–	<0.0001
Medium	233	44	262	49	0.67	0.52	0.87	
Dark	16	3	59	11	0.21	0.12	0.37	
Effect of sun on skin								
Blistered/burnt	185	35	141	26	1.68	1.24	2.27	0.002
Mild burn	169	32	160	30	1.35	1.00	1.83	
Tan	157	30	201	38	1	–	–	
Other	18	3	31	6	–	–	–	
Average cumulative sun exposure (hours per day during summer)[a]								
≤2.4	129	24	137[b]	26	1	–	–	0.30
2.5–3.5	151	29	153	29	1.05	0.75	1.46	
3.6–4.5	135	26	112	21	1.28	0.90	1.81	
≥4.5	112	21	125	24	0.95	0.68	1.35	

*P-value is for the effect of the factor.
[a]Sun exposure was estimated by taking a mean of eight categorical variables measuring average daily exposure to the sun in summer over respondents' lifetimes and categorizing this mean.
[b]For two cases and six controls exposure information was not available.

The trend was observed for both male and female patients, but the effect of genotype on recurrence of BCC did not reach statistical significance. Moreover, no statistically significant difference in age of onset of BCC was observed in cases with different genotypes (Table III). Results in Table IV assess the interaction between BCC risk and skin type, sun-exposure and the *XRCC3* genotypes. The data indicate that the protective effect of the variant T-allele is slightly higher in individuals with light skin complexion than those with medium complexion, but the risk differences did not reach statistical significance. The difference in age of onset was only marginally different between carriers and non-carriers in BCC cases whose skin showed mild burn on sun exposure. No other subgroup showed significant difference in age of onset between carriers and non-carriers.

Discussion

This communication reports genotype distribution of SNPs in seven genes involved in different DNA repair pathways. The number of screened BCC cases and controls resulted in one of the largest association studies that have been carried out to-date. The combination of genotypes with individual data on the effect of sun exposure on skin permitted the assessment of gene–environment interactions (27,28). The variant allele for the T241M *XRCC3* polymorphism was associated with a decreased risk of BCC and with a decreased risk of multiple BCC. A previous study, based on female nurses, found a significant association between the same polymorphism and BCC risk (19). In the present study, the protective effect was observed in both males and females. On the other hand, the variant allele of the E185Q *NBS1* polymorphism was associated with increased risk of BCC in men but not in women. The data also indicated a multiplicative gene–gene (*XRCC3* × *NBS1*) interaction. However, no differentiation in genotype effect was observed due to skin type and complexion.

The present study has its attendant limitations. The multiple-center-based collection of samples could have increased data heterogeneity. Therefore, the estimated genetic effects were adjusted for nationality. Some selection bias due to hospital-based recruitment of controls cannot be ruled out. However, the recruitment process was designed to ensure maximal coverage, and stringent exclusion criteria ensured that controls were not hospitalized owing to arsenic-exposure-related conditions or other tumors. Another limitation of this study was the inclusion of only one polymorphism from each of the seven studied genes. It may be pointed out that the absence of association between the studied genetic variants and BCC risk does not preclude the involvement of other polymorphisms in modulation of BCC susceptibility. One of the problems associated with case–control studies is poor reproducibility (29). In this study, both genotype and allele effects were statistically significant after correction for multiple hypothesis testing by permutation. Furthermore, calculations based on the approach of Wacholder *et al*. (30) estimated that the likelihood of the observed association between BCC risk and *XRCC3* variant being false was <30% (results not shown).

XRCC3 and NBS1 are involved in homologous recombination repair of DNA double strand breaks. *XRCC3* is one of the *RAD51* like gene paralogs and NBS1 forms a multimeric complex with hMRE11/hRAD50 in response to DNA damage (31,32). Functional evaluation of non-synonymous SNPs in DNA repair genes has predicted possible damaging consequences due to the T241M *XRCC3* polymorphism (33). The 241M *XRCC3* variant allele has been associated with higher levels of bulky DNA adducts, but did not show altered sensitivity on treatment of cells with an intra-strand cross-linking miotmycin-C (34,35). The paradoxical protective effect could be due to increased apoptosis as a consequence of less efficient repair (19). The functional consequences of E185Q *NBS1* polymorphism are unknown, but its location within the conserved BRCA1 C-terminus (BRCT) domain may be related to some effect on protein function (36). The homozygote variant allele carriers among lung cancer patients were shown to be associated with significantly increased prevalence of p53 mutations (37). Most genes require bi-allelic inactivation to modulate DNA repair and many proteins

Table II. Genotype and allele frequencies of polymorphisms in DNA repair genes and risk of BCC

	All					Males					Females				
*XPC*K939Q A>C	AA	AC	CC	A-allele	C-allele	AA	AC	CC	A-allele	C-allele	AA	AC	CC	A-allele	C-allele
Controls	179	262	92	620	446	90	141	43	321	227	89	121	49	299	219
Cases	179	258	92	616	442	88	109	40	285	189	91	149	52	331	253
OR[a]	1.00	0.99	0.95	1.00	0.98	1.00	0.80	0.85	1.00	0.90	1.00	1.19	1.06	1.00	1.05
95% CI	–	0.75–1.30	0.66–1.38	–	0.82–1.17	–	0.54–1.20	0.50–1.48	–	0.70–1.17	–	0.81–1.77	0.64–1.75	–	0.82–1.34
P-value[b]			0.97		0.81			0.56		0.44			0.65		0.70
χ^2-trend			0.001					0.25					0.12		
P-trend[c]			0.97					0.61					0.73		
XPD K751Q A>C	AA	AC	CC	A-allele	C-allele	AA	AC	CC	A-allele	C-allele	AA	AC	CC	A-allele	C-allele
Controls	179	262	92	620	446	99	136	50	312	236	89	121	49	308	210
Cases	174	269	86	617	441	78	116	43	272	202	91	149	52	345	239
OR	1.00	1.11	1.05	1.00	1.03	1.00	0.99	1.08	1.00	1.03	1.00	1.24	0.98	1.00	1.04
95% CI	–	0.84–1.46	0.72–1.52	–	0.87–1.24	–	0.66–1.48	0.64–1.64	–	0.79–1.34	–	0.85–1.82	0.58–1.67	–	0.81–1.33
P-value			0.76		0.81			0.93		0.80			0.66		0.78
χ^2-trend			0.005					0.021					0.018		
P-trend			0.94					0.88					0.89		
*XPG*D1104H G>C	GG	GC	CC	G-allele	C-allele	GG	GC	CC	G-allele	A-allele	GG	GC	CC	G-allele	C-allele
Controls	330	173	30	833	233	169	84	21	422	126	161	89	9	411	107
Cases	325	172	32	822	236	148	77	12	373	101	177	95	29	449	135
OR	1.00	1.00	1.10	1.00	1.03	1.00	1.06	0.65	1.00	0.91	1.00	0.97	2.07	1.00	1.14
95% CI	–	0.77–1.31	0.64–1.87	–	0.83–1.27	–	0.71–1.57	0.30–1.38	–	0.67–1.23	–	0.67–1.40	0.90–4.73	–	0.88–1.46
P-value			0.94		0.81			0.47		0.53			0.21		0.32
χ^2-trend			0.059					0.38					0.94		
P-trend			0.80					0.53					0.33		
*XRCC*1 R399Q G>A	GG	GC	CC	G-allele	A-allele	GG	GC	CC	G-allele	C-allele	GG	GC	CC	G-allele	C-allele
Controls	215	252	66	682	384	109	130	35	348	200	106	122	31	334	184
Cases	217	244	68	678	380	105	102	30	312	162	112	142	38	366	218
OR	1.00	0.98	1.08	1.00	1.02	1.00	0.84	0.92	1.00	0.92	1.00	1.15	1.30	1.00	1.14
95% CI	–	0.75–1.28	0.71–1.61	–	0.85–1.23	–	0.57–1.24	0.52–1.63	–	0.71–1.20	–	0.79–1.67	0.74–2.27	–	0.88–1.46
P-value			0.81		0.82			0.68		0.56			0.60		0.32
χ^2-trend			0.003					0.59					0.40		
P-trend			0.95					0.44					0.53		
XRCC3 T241M C>T	CC	CT	TT	C-allele	T-allele	CC	CT	TT	C-allele	T-allele	CC	CT	TT	C-allele	T-allele
Controls	180	265	88	625	441	88	137	49	313	235	92	128	39	312	206
Cases	229	236	64	694	364	99	112	26	310	164	130	124	39	384	200
OR	1.00	**0.71**	**0.54**	1.00	**0.73**	1.00	**0.71**	**0.43**	1.00	**0.68**	1.00	**0.70**	**0.66**	1.00	**0.78**
95% CI	–	**0.54–0.92**	**0.36–0.80**	–	**0.61–0.88**	–	**0.48–1.05**	**0.24–0.77**	–	**0.52–0.88**	–	**0.48–1.02**	**0.39–1.13**	–	**0.61–1.01**
P-value			**0.003**		**0.0007**			**0.01**		**0.004**			**0.12**		**0.06**
χ^2-trend			**10.96**					**7.5**					**3.53**		
P-trend			**0.0009**					**0.006**					**0.06**		
NBS1 E185Q G>C	GG	GC	CC	G-allele	C-allele	GG	GC	CC	G-allele	C-allele	GG	GC	CC	G-allele	C-allele
Controls	250	221	62	625	441	136	113	25	385	163	114	108	37	336	182
Cases	226	229	74	694	364	97	100	40	294	180	129	129	35	387	199
OR	1.00	1.15	1.34	1.00	1.16	1.00	1.25	**2.19**	1.00	**1.44**	1.00	1.07	0.84	1.00	0.96
95% CI	–	0.88–1.50	0.90–1.94	–	0.97–1.40	–	0.85–1.84	**1.23–3.91**	–	**1.10–1.88**	–	0.74–1.55	0.49–1.47	–	0.74–1.24
P-value			0.29		0.11			**0.03**		**0.008**			0.69		0.76
χ^2-trend			2.40					**7.24**					0.16		
P-trend			0.12					**0.007**					0.69		
APEX1 D148E T>G	TT	TG	GG	T-allele	G-allele	TT	TG	GG	T-allele	G-allele	TT	TG	GG	T-allele	G-allele
Controls	148	257	128	553	513	73	135	66	281	267	75	122	62	272	246
Cases	142	264	123	548	510	64	114	59	242	232	78	150	64	306	278
OR	1.00	1.08	0.99	1.00	1.00	1.00	0.93	0.99	1.00	0.99	1.00	1.21	0.97	1.00	0.99
95% CI	–	0.80–1.45	0.70–1.40	–	0.84–1.19	–	0.61–1.43	0.60–1.64	–	0.77–1.28	–	0.80–1.82	0.60–1.58	–	0.78–1.27
P-value			0.83		0.97			0.94		0.97			0.52		0.96
χ^2-trend			0.001					0.005					0.001		
P-trend			0.97					0.94					0.97		

[a]ORs were estimated by logistic regression and are adjusted for age, gender and nationality.
[b]*P*-values calculated are for genotype (in genotype columns) and allele effects (in allele columns).
[c]*P*-trend are from trend test using three genotypes as inordinate (0, 1 and 2) variables.
Bold faces indicate significant associations.

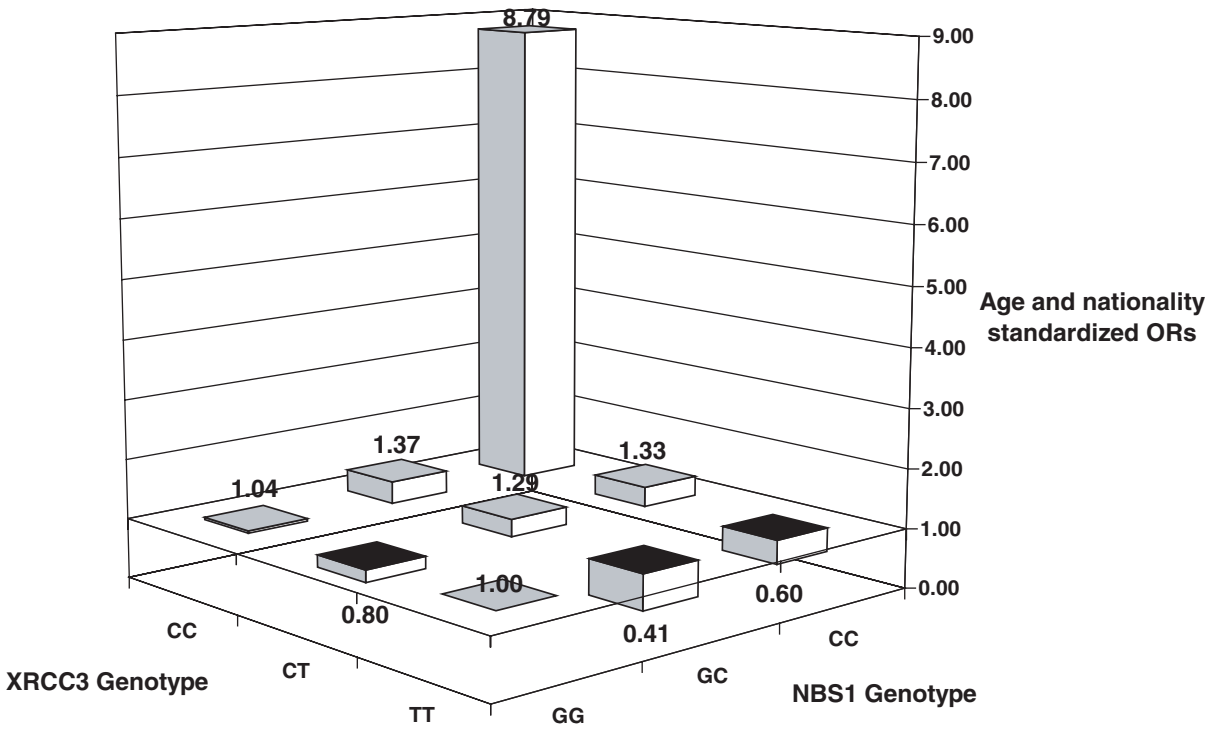

Fig. 1. Risk associated with different combinations of *NBS1* and *XRCC3* genotypes in male BCC cases compared with male controls. Low-risk genotype combination (GG-genotype in *NBS1* for Q185E polymorphism and TT-genotype in *XRCC3* for T241M polymorphism) was used as a reference.

Table III. Effect of the *XRCC*3 genotypes on the recurrence and the onset age of BCC

XRCC3 genotype	*N*1[a]	Multiple BCC[b]				Age at onset of BCC		
		*N*2	OR	95% CI	*P*	Median	5th and 95th percentiles	*P*[c]
All								
CC	229	39	1			64	41, 78	0.29
CT	236	32	0.86	0.50–1.48	0.86	66	44, 78	
TT	64	8	0.89	0.38–2.11		68	45, 77	
Men								
CC	99	17	1			65	41, 78	0.55
CT	112	17	0.87	0.40–1.89	0.92	67	43, 79	
TT	26	4	1.10	0.30–3.75		70	49, 78	
Women								
CC	130	22	1			64	41, 78	0.52
CT	124	15	0.82	0.38–1.76	0.85	66	44, 76	
TT	38	4	0.78	0.23–2.58		68	44, 77	

[a]*N*1 is the number of BCC cases and *N*2 is the number of cases with multiple BCCs.
[b]Adjusted for age, sex and nationality.
[c]*P*-values from Kruskal–Wallis tests.

Table IV. ORs and age of onset of BCC for carriers of variant allele for T241M polymorphism in *XRCC3* versus non-carriers, according to skin type and effect of sun on skin

OR[a] (Carriers versus non-carriers)		95% CI	*P*	Median age of onset		*P*[b]
				Non-carriers	Carriers	
Complexion						
Light	0.63	0.42–0.92	0.18[c]	63	64	0.80
Medium	0.69	0.47–1.01		63	65	0.17
Effect of sun on skin						
Blistered/burnt	0.66	0.41–1.07	0.41[d]	61	62	0.91
Mild burn	0.74	0.45–1.19		60	64	0.04
Tan	0.78	0.49–1.24		64	66	0.97

[a]ORs and 95% CIs were adjusted for gender, nationality and age (as a continuous variable), complexion and effect of sun on skin.
[b]*P*-values from Mann–Whitney tests.
[c]Interaction *XRCC3* carrier status × complexion.
[d]Interaction *XRCC3* carrier status × effect of sun on skin.

interact in DNA repair processes (38). Considering the range of involvement of NBS1 in cellular processes, the observed multiplicative interaction with *XRCC3* may be attributable to a functional cooperation. The observed gender-specific effect would require further independent confirmation.

In conclusion, among the seven DNA repair genes analyzed in this study, only polymorphisms in *XRCC3* and *NBS1* were associated with BCC risk. The increased risk due to the variant allele for E185Q *NBS1* polymorphism was seen only in men. In addition, carriers of the variant allele for the T241M *XRCC3* polymorphism were at reduced risk of multiple BCC.

Supplementary material

Supplementary material are available at *Carcinogenesis* Online

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