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Polymorphisms in *RAI* and in genes of nucleotide and base excision repair are not associated with risk of testicular cancer

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Abstract

Testicular cancer has been suggested to be primed in utero and there is familiar occurrence, particularly brothers and sons of men with testicular cancer have increased risk. Although no specific causative genotoxic agents have been identified, variations in DNA repair capacity could be associated with the risk of testicular cancer. A case–control study of 184 testicular cancer cases and 194 population-based controls living in the Copenhagen Greater Area in Denmark was performed. We found that neither polymorphisms in several DNA repair genes nor alleles of several polymorphisms in the chromosomal of region 19q13.2-3, encompassing the genes *ASE*, *ERCC1*, *RAI* and *XPD*, were associated with risk of testicular cancer in Danish patients. This is in contrast to other cancers, where we reported strong associations between polymorphisms in *ERCC1*, *ASE* and *RAI* and occurrence of basal cell carcinoma, breast cancer and lung. To our knowledge this is the first study of DNA repair gene polymorphisms and risk of testicular cancer.

1. Introduction

Testicular cancer occurs most often before age 50. Testicular cancer can arise from several different cell types. The most common (and aggressive) kind of testicular cancer is the germ cell tumors. Germ cell tumors may be either seminomas (the most common type) or non-seminomatous tumors (including embryonal cell cancers, choriocarcinomas and teratomas). The incidence rate of new cancers appears to be increasing worldwide among Caucasian males but not among other racial groups. Geographic variation in the occurrence of the testicular cancer has been noted with higher risks observed in Germany, Switzerland, Scandinavia, and New Zealand. Lowest rates are seen in Asia and Africa. Geographic clustering of testicular

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germ-cell tumors and racial differences in the incidence of this disease could indicate a genetic component in the cause of this disease [1]. Indeed, brothers and sons of men with testicular cancer have 7–10- and 4-fold increased risk of testicular cancer, respectively [2].

More than 95% of the testicular cancer cases are considered to be germ cell-derived and it has been postulated that the disease may be a consequence of early exposure, possibly already in utero [3]. An association between lung cancer in women and risk of testicular cancer in their sons have suggested that exposure in utero to maternal smoking may be a risk factor [4]. However, one case–control study did not find such an association and another case–control study actually found an inverse association between maternal heavy smoking and the son's risk of testicular cancer [5,6]. Quitting smoking was not found to result in a reduction of risk [5]. Furthermore, there is evidence, that exposure to maternal hormones, particularly estrogens, is associated with testicular germ-cell cancer risk [7].

It has been suggested that SNPs in certain DNA-repair genes, especially in *XPD*, *XPC* and *XRCC3* are associated with modified DNA repair capacity and/or higher DNA adduct levels [8,9]. A number of case–control studies concerning the DNA repair genes *XPA*, *XPD*, *XPC*, and *ERCC1* (nucleotide excision repair), *OGG1* (base excision repair), and *XRCC3* (homologous recombination of double strand breaks) have been published [10]. The results of these studies indicate that inherited variation in DNA repair capacity is an important risk factor for several cancer types.

The gene *RAI* is situated between *ERCC1* and *XPD*. *RAI* is an inhibitor of the RelA subunit of the transcription factor NF-κB, which is involved in control of inflammation and apoptosis. It is, therefore, likely that polymorphisms affecting the level or activity of the RelA-associated inhibitor RAI would influence the availability of RelA, and thus modify regulation of apoptosis. We have recently shown that several SNPs in this region are associated with increased risk of skin cancer [11–13] breast cancer [14] and lung cancer [13]. In particular, SNPs in *RAI* have showed persistent associations with cancer risk. One polymorphism in *RAI* was associated with a 12.3-fold increased risk of non-melanoma skin cancer before age 50 ($P<0.00009$), and we subsequently identified a high-risk haplotype encompassing this polymorphism. Homozygous carriers of this haplotype were at 9.5-fold increased risk of breast cancer (CI = 2.21–40.79, $P=0.003$) before age 55, and at 4.9-fold increased risk of lung cancer before age 56 (CI = 1.58–15.32, $P=0.006$) [14,15].

Basal cell carcinoma patients have increased risk of several cancer forms including breast cancer (women), lung cancer (for men and women), prostate cancer and testis (men) [1]. Since, these cancer forms are unlikely to share environmental risk factors it is very likely that they share genetic risk factors. It is possible that the previously mentioned high-risk haplotype would be associated with risk of testicular cancer because this haplotype seems to be a marker of general mechanism affecting several cancer forms.

Various studies have suggested that certain DNA repair proteins are present in sperm and sperm precursor cells [16]. It seems that levels tend to be lower in tumor testicular cells [17]. This can be construed as an argument that repair gene expression protects against formation of the tumors.

In the present paper, we aimed to evaluate whether the recently identified high-risk haplotype was also associated with increased risk of testicular cancer in the Danish population. In addition, we included several other polymorphisms in genes of nucleotide and base excision repair. We report that no association was found between the studied polymorphisms and risk of testicular cancer.

2. Materials and methods

2.1. Study groups

A population-based case–control study of testicular cancer among Danish men has been performed and some data have been published previously [16,17]. Cases of histologically verified testicular cancer were identified from the Danish Cancer Registry, which is considered more than 95% complete, and from the in-patients files of the oncological departments in the Greater Copenhagen Area. Additional eligibility criteria included: unilateral testicular cancer, time of diagnosis January 1, 1989 to June 30, 1993, age 18–45 years at time of diagnosis, at least 6 month elapsed

since any radiation or chemotherapy, Caucasian race, Denmark as place of birth, alive and living in the Greater Copenhagen area.

The cases were classified as seminoma or non-seminoma according to the histological diagnosis of the tumors. For each group of cases, a group of male controls matched for the year of birth was drawn at random from the Danish National Population Registry. The eligibility criteria of the controls included: Caucasian race, Denmark as the place of birth, alive and living in the Greater Copenhagen area at the time of participations. Two hundred and twenty-eight cases and 327 controls were asked by letter to participate. One hundred and eighty-four cases and 194 controls actually participated.

All participants gave information regarding height, weight, their consumption of alcoholic beverages, coffee, tea, cola, the duration of exercise during the preceding 2 weeks, the ingestion of drugs and whether they suffered from cryptorchidism in their childhood [18,19].

DNA for the analysis was isolated from full blood or plasma. The blood samples were collected with ethical permission and all participants have given their consent. Genotyping of the listed genes has been approved by the Danish Scientific Ethical Committee.

2.2. Detection of single nucleotide polymorphism

The studied SNPs are listed in Table 1. Genotypes of all mentioned polymorphisms were detected using LightCycler (Roche Molecular Biochemicals, Mannheim, Germany) or a ABI 7700 (Applied Biosystems, Naerum, Denmark). We determined the polymorphisms by Lightcycler in cohort, using the following primers and probes:

ERCC1 N118N. Forward 5′ GAC CAC AGG ACA CGC AGA; reverse 5′ TTC CTG AAG TCT GGG GTG G; sensor 5′-CgC AAC GTG CCC TGG GAA T X; anchor 5′-LC Red640-TGG CGA CGT AAT TCC CGA CTA TGT GCT G p. The LightCycler reaction mix (total vol. 10 μl/tube), contained: 0.25 μl of Advance Taq Polymerase (5 U/μl); 1 μl of 10× Adv. Taq Polymerase Buffer; 0.13 μl of 10 mM dNTPs; 0.1 μl of the forward primer (100 pmol); 0.1 μl of the reverse primer (100 pmol), 0.05 μl of the anchor (20 mM), 0.05 μl of the sensor (20 mM), 0.5 μl of 100% DMSO; 4.82 μl of H20, and 1 μl of DNA. After initial denaturation of 30 s at 95 °C, the main program for LightCycler assay contained 45 cycles of 2 s at 95 °C, 20 s at 57 °C, and 25 s at 72 °C.

Ase-1 G-21A, *OGG1 S326C*, *XPD K751Q*, *XPD D312N*, *XPD R156R*, *XPC K939Q*, *XRCC3 IV S6 C1571* and *RAI IV S1 A4364* genotypes were determined by real-time PCR on an ABI 7700 (Applied Biosystems, Naerum, Denmark). Controls were included in each run, and 10% of the samples were typed twice with identical results.

XPD D312N. Probes were: G-allele: 5′-Fam-CTG CCC GAC GAA G-MGB, A-allele: 5′Vic-TGC CCA ACG AAG TG-MGB, primers: 5′-CCG CAG GAT CAA AGA GAC AGA-3′, 5′-CCT CTG CGA GGA GAC GCT AT-3′. Ten-microliter reactions contained 100 nM G-allele-specific probe, 120 nM A-allele-specific probe, 800 nM

Table 1
Polymorphisms used in this study, their kind and their positions

SNP name	Kind	dbSNP#	Trivial name	Chromosome	Sequence	Position in sequence	Relative position
Markers on chromosome 19q13.2-3							
XPD K751Q	A/C	Rs1052559	XPD exon 23	19	NT_011109	18123137	0
XPD D312N	A/G	Rs1799793	XPD exon 10	19	NT_011109	18135477	12340
XPD R156R	C/A	Rs238406	XPD exon 6	19	NT_011109	18136527	13390
RAI INS1, A4364G	A/G	Rs1970764	RAI intron 1	19	NT_011109	18159091	35954
ASE-1, G-21A	A/G	Rs967591	ASE-1 exon 4	19	NT_011109	18178152	55015
ERCC1 N118N	C/T	Rs861535	ERCC1 exon4	19	NT_011109	18191871	68734
Other DNA repair markers							
XRCC3 IVS6 C1571T	T/C	Rs861535	XRCC3	14	NT_026437	84087979	
OGG1 S326C	C/G	Rs1052134	OGG1_326	3	NT_022517	9738774	
XPC K939Q	A/C	Rs2228001	XPC	3	NT_022517	14127450	

primers in 1× Mastermix. The reactions were run for 40 cycles at 15 s at 94 °C, 60 s at 62 °C.

RAI INS1 A4364G. Probes were: A-allele: 5′-FAM-ATC GCA CCA CTG CA-3′-MGB, G-allele: 5′-VIC-AGA TCG CGC CAC TG-3′-MGB. Primers were: 5′-GGC GGA GCT TGC AGT GA-3′, 5′-CTA TGA TGG AGA ACT TTA ATA TTT TTC TGT TAG-3′. Ten-microliter reactions contained 100 nM probes, and 800 nM primers in 1× Mastermix.

The reactions were run for 40 cycles at 15 s at 94 °C, 60 s at 62 °C.

XPD R156R was genotyped as previously described [14] *XPD K751Q* and *ASE-1 G-21A* were determined as described [15].

XPC Lys939Gln (*XPC A2920*) (rs#2228001). Primers were: XPC exon 15 F: 5′-TGG GCC CAA GAA GAC CAA-3′, XPC exon 15 R: 5′-TGG GTG CCC CTC TAG TGG-3′. Probes: A-allele: 5′-VIC-TCC CAT TTG AGA AGC TGT GAG-TAMRA-3′, C-allele: 5′-FAM-TTC CCA TTT GAG CAG CTG TGA GC-TAMRA-3′. Ten-microlitre reactions contained 100 nM of each probe, 900 nM primers, 50 ng DNA and 1× Mastermix (Applied Biosystems, Naerum, Denmark). The reactions were run for 40 cycles at 15 s at 94 °C, 60 s at 63 °C.

OGG1 S326C was determined as previously described [22].

XRCC3 IVS6 C1571T was determined as previously described [23].

2.3. Statistics

Data recording and calculation and tests of allele frequencies were performed in SPSS and Excel. Tests for association of individual markers with testicular cancer were performed by χ^2-tests of allele frequencies using SPSS program (SPSS, Inc., Chicago, IL). To calculate odds ratios and related parameters, Excel (Microsoft, Redmond, WA) program was used. The power calculations were performed using SamplePower (SPSS, Inc., Chicago, IL).

3. Results

This case–control study of testicular cancer among Danish males was based on 184 cases and 194 population-based controls matched on age and gender. Of the cases 80 were seminomas and 104 were non-seminomas. The average age was 35.7 years among the cases. We have searched for an association of testicular cancer with six SNPs on chromosome 19q13.2.3 as well as three SNPs in other repair genes. The SNPs are listed in Table 1. The studied polymorphisms were all in Hardy–Weinberg equilibrium in the control group. Our main goal was to investigate, if there was any association between a previously described high-risk haplotype and occurrence of testicular cancer. No association between genotype and risk of testicular cancer was observed (Table 2). The high-risk haplotype gave an almost significant result in a one-sided Fisher's test ($P = 0.062$), but as we did not apply Bonferroni corrections, the additional use of one-sided tests seems overly optimistic. None of the other analyzed SNPs were associated with risk of testicular cancer (Table 2).

4. Discussion

We here report that we have been unable to find any association between markers located on chromosome 19q13.2-3 and risk of testicular cancer. This result was obtained both when we treated all testicular germ cell tumors as one, and when we subdivided the cancers into seminomas and non-seminomas (results not shown). Power calculation shows that we had a 47% chance of detecting an OR = 2 at 5% level and a 99% chance of detecting an OR = 4 at 1% level, if we use the frequency of the high risk haplotype in the controls as starting value. Thus, we had amble power to detect OR = 5–10 which were the ORs we have previously found for the association between the high-risk haplotype and risk of breast and lung cancer in the age interval 50–60 years [14–15]. However, this calculation and the upper limits on the confidence intervals listed in Table 2 indicate that ORs of approximately 2 could be present in the population without registering in our analysis.

The region of chromosome 19, which we have investigated, contains four genes: *XPD*, *RAI*, *ASE-1* and *ERCC1*. Of these *XPD* and *ERCC1* are well known genes in nucleotide excision repair, *RAI* appears to be a modulator of NF-κB and possibly

Table 2
Frequencies of testicular cancer in various genotypes of the investigated SNPs

SNP name	SNP genotypes	Controls	Cases	*P*-value[a]	OR (CI)	OR (CI)[b]
Markers on chromosome 19q13.2-3						
XPD K751Q	AA	74	70	0.736	1.0	1.0
	AC	99	90		0.96 (0.62–1.48)	
	CC	18	21		1.23 (0.61–2.51)	1.00(0.66–1.52)
XPD D312N	GG	84	81	0.919	1.0	1.0
	GA	95	87		0.95 (0.62–1.45)	
	AA	12	12		1.04 (0.44–2.44)	0.96 (0.64–1.45)
XPD R156R	CC	49	37	0.229	1.0	1.0
	AC	95	94		1.31 (0.78–2.19)	
	AA	46	50		1.44 (0.80–2.58)	1.35 (0.83–2.20)
RAI INS1 A4364G	AA	121	110	0.957	1.0	1.0
	AG	59	63		1.17 (0.76–1.82)	
	GG	10	6		0.66 (0.23–1.88)	1.10 (0.72–1.68)
ASE-1 G-21A	GG	137	134	0.663	1.0	1.0
	AG	46	41		0.91 (0.56–1.48)	
	AA	6	5		0.85 (0.25–2.86)	0.90 (0.57–1.44)
ERCC1 N118N	AA	78	84	0.610	1.0	1.0
	AG	99	77		0.72 (0.47–1.10)	
	GG	14	18		1.19 (0.56–2.56)	0.78 (0.52–1.18)
Haplotype of the above						
High risk[c]	No	148	126	0.098	1.0	
	Yes	41	52		1.49 (0.93–2.39)[d]	
Other DNA repair markers						
XRCC3 IVS6 C1571T	TT	155	140	0.249		1.0
	CT	34	36		1.17 (0.70–1.97)	
	CC	2	5		2.77 (0.53–14.5)	1.26 (0.76–2.08)
OGG1 S326C	CC	119	113	0.944	1.0	1.0
	CG	63	60		1.00 (0.65–1.55)	
	GG	9	8		0.94 (0.35–2.51)	0.99 (0.65–1.51)
XPC K939Q	AA	68	70	0.336	1.0	1.0
	AC	93	88		0.92 (0.59–1.43)	
	CC	30	22		0.71 (0.37–1.36)	0.87 (0.57–1.32)

[a] *P*-value for the trend.
[b] Odds ratio of common homozygote against heterozygote plus rare homozygotes.
[c] Homozygotes for the haplotype RAI INS1 A4364G^{A} ASE-1 G-21A^{G} ERCC1 N118N^{A}.
[d] Odds ratio between homozygote carriers and all others for the high risk haplotype.

p53 [20,21] most likely as a regulator of apoptosis. The last gene *ASE-1* appears to be involved in the regulation of transcription of ribosomal RNA. Thus, the region seems to be involved in the balance between growth and elimination of DNA damage and unwanted cells.

Our finding that occurrence of testicular cancers is not influenced by chromosome 19q13.2-3 or the other tested DNA repair genes suggests that the underlying mechanism inducing this cancer form differs from that of the other mentioned cancers, and does not to the same extent involve DNA damage repaired by nucleotide excision or base excision. Testicular cancer occurs at a relatively early age, typically before age 50, whereas risks for the other cancers typically increase throughout life. Possibly, testicular cancer is more related to developmental defects, as it is for instance well known to be associated with cryptorchidism as also shown in the present material [6,18]. Moreover, the risk remains high even when this condition is surgically corrected. Thus, exposures in utero are thought to be relevant for the risk of testicular cancer. So far, only hormonal influence seems to be important [7], whereas maternal smoking

was not shown to be a risk factor in case control studies [5]. This is in accordance with the present data showing no sign of association between risk of testicular cancer and polymorphisms in enzymes of nucleotide and base excision repair, which would have been expected to modify the effect of many genotoxic exposures.

In conclusion, the present population-based case–control study did not show any significant signs of associations between the risk of testicular cancer and polymorphisms in several genes coding for DNA repair enzymes and other relevant genes located on chromosome 19q13.2-3, which have previously shown associations with several other cancer forms.

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