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Genetic Variation in DNA Repair Genes and Prostate Cancer Risk: Results from a Population-Based Study

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Abstract

Objective—DNA repair pathways are crucial to prevent accumulation of DNA damage and maintain genomic stability. Alterations of this pathway have been reported in many cancers. An increase in oxidative DNA damage or decrease of DNA repair capacity with aging or due to germline genetic variation may affect prostate cancer risk.

Methods—Pooled data from two population-based studies (1,457 cases and 1,351 controls) were analyzed to examine associations between 28 SNPs in 9 DNA repair genes (*APEX1*, *BRCA2*, *ERCC2*, *ERCC4*, *MGMT*, *MUTYH*, *OGG1*, *XPC*, and *XRCC1*) and prostate cancer risk. We also explored whether associations varied by smoking, by family history or clinical features of prostate cancer.

Results—There were no associations between these SNPs and overall risk of prostate cancer. Risks did not vary either by smoking or by family history of prostate cancer. Although, two SNPs in *BRCA2* (rs144848, rs1801406) and two SNPs in *ERCC2* (rs1799793, rs13181) showed stronger associations with high Gleason score or advanced stage tumors when comparing homozygous men carrying the minor vs. major allele, results were not statistically significantly different between clinically aggressive and non-aggressive tumors.

Conclusion—Overall this study found no associations between prostate cancer and the SNPs in DNA repair genes. Given the complexity of this pathway and its crucial role in maintenance of genomic stability a pathway-based analysis of all 150 genes in DNA repair pathways, as well as exploration of gene-environment interactions may be warranted.

Keywords

DNA repair; SNPs; prostate cancer; case-control study; genetic variation

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Introduction

Prostate cancer is the most commonly diagnosed solid tumor and the second leading cause of cancer-related deaths among men in the U.S. (1). It is a multi-factorial disease, where both genetic and environmental factors contribute to disease incidence (2). The exponential increase in risk of prostate cancer associated with aging may reflect the accumulation of DNA damage as a result of a series of processes including oxidative stress, inflammation or environmental carcinogens or a decrease in DNA damage-repair response capacity (3–5). An increase in generation of reactive oxygen species from metabolism of endogenous (e.g., androgens, inflammation) and exogenous (e.g., dietary meat, fat, environmental toxins) compounds within the prostate cells can produce DNA adducts or directly damage DNA (4–7). In support of this hypothesis, several studies have reported that DNA adducts are formed in the prostate tissue as a result of exposure to oxidative stress or environmental toxins particularly heterocyclic amines (derived from red meat mutagens) and polycyclic aromatic hydrocarbons (8–10).

DNA repair mechanisms are important pathways in removal of oxidative DNA compounds or DNA adducts from damaged genomic sites (11). There are a number of DNA repair pathways, each responsible for repairing a different type of DNA damage. Base excision repair removes single base modifications including single strand breaks, oxidative DNA damage and non-bulky adducts, where as nucleotide excision repair removes larger lesions, which often result from environmental exposures such as smoking, UV radiation or external carcinogens (11, 12). Alkyltransferases directly reverse DNA damage by transferring alkyl groups from damaged DNA onto the transferase enzyme (11). Finally, double-strand DNA breaks are repaired through complex mechanisms including homologous recombination and end-joining repair pathways (13,14). Germline genetic variation in the above DNA repair genes/pathway, which may affect the capacity of encoded DNA repair enzymes to effectively remove DNA adducts or lesions, may result in enhanced cancer risk (15–18).

Several epidemiologic studies have examined associations between single-nucleotide polymorphisms (SNPs) in DNA repair genes, mostly non-synonymous SNPs with potential functional significance, and risk of prostate cancer (17,19–26). However, results have been inconsistent across these studies due in part to different study populations, case ascertainment, or due to small sample sizes of each study and thus the potential for false-positive findings as well as limited power to detect modest associations. The objective of our study was to examine associations between genetic variants in DNA repair genes and risk of prostate cancer in a large population-based case-control dataset, with detailed information on demographic and lifestyle factors, screening as well as clinical features of the disease. In addition, we were interested in exploring whether SNP-prostate cancer associations varied according to smoking status, family history of prostate cancer, or clinical features of this cancer.

Materials and Methods

Study Population

Study subjects were Caucasian and African American men residing in King County, Washington, who participated in one of two population-based case-control studies of prostate cancer with ascertainment periods from 1993 to 1996 and 2002 to 2005 that have been previously described (27,28). Incident cases with histologically confirmed adeno-carcinoma of the prostate were 35 to 74 years old at diagnosis, and were identified via the Seattle-Puget Sound Surveillance, Epidemiology, and End Results (SEER) cancer registry. The SEER cancer registry also provided information on clinical characteristics of prostate cancer including Gleason score, tumor stage, and serum prostate-specific antigen (PSA) levels at diagnosis, as well as primary treatment for prostate cancer. Controls were men without a self-reported physician's diagnosis of prostate cancer, identified via random digit dialing, frequency matched

to cases by 5-year age groups, and recruited evenly throughout the ascertainment period of the cases. Both studies were approved by the Institutional Review Board (IRB) of the Fred Hutchinson Cancer Research Center, and written informed consent was obtained from all study participants. Genotyping was approved by the IRB of the National Human Genome Research Institute.

Study subjects completed a structured in-person interview administered by trained male interviewers. The questionnaire collected information about demographic, social and lifestyle characteristics, medical history including prostate cancer screening, as well as information about family history of prostate cancer. After the interview, participants were asked to provide a blood sample. Of the combined 2,244 eligible prostate cancer cases and 2,448 eligible controls identified in the two population-based studies, 1,754 (78.2%) cases and 1,645 (67.2%) controls agreed to participate and were interviewed. Among men who participated, 1,457 (83.1%) cases and 1,351 (82.1%) controls provided a blood sample, which was used to obtain germline DNA for genotyping.

Selection of SNPs and Genotyping

SNPs in DNA repair genes were selected for genotyping in this study based on the following criteria: (a) functional significance, as assessed by potential effects on enzyme level activity or projected influence on DNA adducts levels, (b) previously reported association(s) with prostate cancer risk in earlier studies, (c) tagSNPs with a minor allele frequency ≥5% selected from available HapMap (version 3.1), dbSNP (http://www.ncbi.nlm.nih.gov/projects/SNP/) and Genome Variation Server (http://pga.gs.washington.edu/gvs). The majority of the SNPs in 9 DNA repair genes genotyped in our study were non-synonomous SNP (n=13) followed by synonomous SNPs (n=8), SNPs located in the UTR region (n=4) and intronic SNPs (n=4). Of the 28 SNPs successfully genotyped, 21 were tagging SNP; however, the coverage of variation across large genes such as *BRCA2 or MGMT* is small. SNPs with prior evidence from association analyses reported from other studies were included, except for the SNPs in the mismatch DNA repair pathway, which were part of another analysis. Potential functional prediction of SNPs that resulted in amino-acid changes was assessed using *in silico* classification program Polyphen (29).

Genomic DNA was purified from peripheral lymphocytes using standard protocols (30). The Applied Biosystems (ABI) SNPlex™ Genotyping system was used for genotyping and GeneMapper software was used for calling alleles. Discrimination of the specific SNP allele was carried out with the Applied Biosystems 3730xl DNA analyzer and was based on the presence of a unique sequence assigned to the original allele-specific oligonucleotide. Quality control included genotyping of 140 blind duplicate samples that were distributed across all genotyping batches. Each batch of DNA aliquots that were genotyped incorporated similar numbers of cases and controls samples collected in a specific calendar year (e.g. 2003) and samples were distributed equally across the entire genotyping plates. The laboratory personnel that performed genotyping were however blinded to the case-control status of the samples.

Initially 35 SNPs in 10 DNA repair genes were selected. Of these, 4 SNPs (*APEX1* rs2307486, *MUTYH* rs3219489, *XRCC1* rs3547, *XRCC3* rs861539) failed on the genotyping platform, and two others (*ERCC4* rs1799802, *MGMT* rs2308318) were monomorphic in our study population. One SNP (rs1052133) in the *OGG1* had a drop-out rate of 9.5%, and thus was excluded from all statistical analyses. The remaining 28 SNPs in 9 DNA repair genes with an average drop-out of 0.6% and an average genotype concordance of 99.7% across 140 blind duplicate samples were included in statistical analyses.

Statistical Analyses

Deviation of genotype frequencies from Hardy-Weinberg Equilibrium (HWE) among Caucasian and African-American controls considered separately was assessed by $\chi 2$-tests (31). Unconditional logistic regression was used to examine associations between SNP genotypes and prostate cancer risk among Caucasian and African-American men and to compute odds ratios (OR) and 95% confidence intervals (CI) (32). Confounding by established and potential risk factors for prostate cancer was assessed for each genotype separately, fitting models using each main effect and then evaluating the change in parameter estimates of the SNP genotypes when other variables entered the models one at a time. All analyses were adjusted for age at diagnosis for cases and at reference date for controls. Further adjustment for a first-degree family history of prostate cancer, history of screening for prostate cancer (PSA and DRE tests) and smoking did not change the risk estimates and thus were not included in the final models. Both additive and dominant genetic models were considered for each variant allele depending on the distribution of genotypes. Likelihood ratio-based test statistics were used to identify statistically significant associations between SNP genotypes and prostate cancer risk.

A permutation procedure was used to account for the effect of multiple testing. Pairs of case-control labels and ages were permuted in order to approximate the distribution of the age-adjusted p-values under the null hypothesis. For each permutation codominant and dominant models were fit for all SNPs and the minimum of these p-values were kept for each SNP. The p-values were then ordered to approximate the null distribution of the order statistics for the p-values, starting from the smallest to the largest. The original p-values were also ordered and permutation p-values were calculated by comparing the ordered p-values to the null distribution for the appropriate order statistic. Permutation p-values can be interpreted as the probability of observing a p-value less than or equal to what was observed for the given order statistic under the null hypothesis of no association with disease for any of the 28 SNPs. The permutation approach to approximating the null distribution of the order statistics will be valid regardless of any correlation between the SNPs. A SNP was considered to be significantly associated with prostate cancer risk if the nominal p-value and the permuted p-value were both <0.05.

In addition, interactions between SNP genotypes and first-degree family history of prostate cancer (yes vs. no) or between base- or nucleotide excision repair genes and either smoking status or lifetime pack-years of smoking were examined in relation to prostate cancer risk. Interactions were tested by including an interaction term in the logistic regression models and comparing the fully saturated model containing the main effects and interaction term with the reduced model containing only the main effects using a likelihood ratio test to determine statistical significance of the interaction effects (33). Lastly, we also examined associations between SNP genotypes and clinical characteristics of prostate cancer. With respect to the Gleason score analyses, cases were grouped into those with Gleason scores of 2–6 or 7=3+4, and those with Gleason scores of 7=4+3 or 8–10 at diagnosis. For cancer stage, cases diagnosed with regional or distant stage were compared to men with localized stage at diagnosis. The frequency of genotypes for DNA repair SNPs in each group of cases was compared to the frequency of genotypes in controls using polytomous logistic regression models (34); these final models were adjusted for age and prostate cancer screening history.

Results

Selected characteristics of prostate cancer cases and controls, stratified by race, are presented in Table 1. The distribution of age was similar between Caucasian cases and controls; however, among African Americans cases were slightly older than controls (p=0.0002) although this could have been due to small number of cases and controls in this category. In both racial groups, cases were more likely than controls to report a first-degree family history of prostate

cancer and to have undergone PSA screening within the 5 year-period before diagnosis or reference date. Cases and controls were similar with respect to other factors including body mass index, education and smoking. With respect to clinical features, the majority of prostate cancer cases were diagnosed with localized stage or Gleason score 2–6 or 7(3+4) cancers and the distribution of Gleason score and tumor stage was similar between cases ascertained in two different periods: 1993–1996 and 2002–2005 (data not shown).

All 28 SNPs evaluated in this study were in HWE among both Caucasian and African Americans controls (all p>0.05). Table 2 presents associations between SNP genotypes and risk of prostate cancer in Caucasians and African-Americans, separately. In single SNP analyses, modest associations with overall risk of prostate cancer were observed in Caucasians for *BRCA2* rs1801406 (OR=0.81; 95% CI 0.69–0.95; comparing any G allele vs. homozygous A allele carriers) and *ERCC2* rs1799793 (OR=0.70; 95% CI 0.54–0.91; comparing men with AA vs. GG genotype). In African-Americans there was an association between prostate cancer and *BRCA2* rs543304 where men with any C allele had an OR=0.54 (95% CI 0.30–0.99) in comparison to men with the TT genotype. However, after adjusting for multiple comparisons the permuted *P*-values of associations between these three SNPs and risk of prostate cancer were no longer statistically significant.

Next we explored interactions between DNA repair SNPs and first-degree family history of prostate cancer (yes vs. no) and smoking (both smoking status and lifetime pack-years of smoking) in relation to prostate cancer risk. There was no evidence for effect modification (data not shown). Lastly, we examined associations between DNA repair SNPs and clinical characteristics of prostate cancer including Gleason score and tumor stage among Caucasians (Table 3). With respect to clinical features of this disease two SNPs (rs144848, rs1801406) in *BRCA2* and two SNP (rs1799793, rs13181) in *ERCC2* showed some associations with Gleason score or tumor stage in single SNP analyses. For *BRCA2* rs144848, although men with the GG genotype had an OR of 1.83 (95% CI 1.09–3.08) of high Gleason score tumors in comparison to men with the TT genotype, the risk estimate was not statistically significantly different in comparison to the OR obtained for tumors with Gleason score 2–6 or 7(3+4) (OR=1.32, p-value for differences in ORs estimates=0.22). For *BRCA2* rs1801406 and *ERCC2* rs1799793, although men homozygous for the minor allele had a slightly stronger reduction in risk of high Gleason score tumors in comparison to men homozygous for the major allele (ORs of 0.48 and 0.54, respectively) the risk estimates between higher and lower Gleason score tumors were not statistically significantly different. Similar findings of no significant differences were also observed in relation to tumor stage when data were stratified according to localized tumors versus regional/distant tumors. No associations were observed between the remaining 24 SNPs in DNA repair genes and any of the clinical characteristics of prostate cancer.

Discussion

In this population-based study we examined associations between 28 SNPs in 9 DNA repair genes and prostate cancer risk among 1,457 cases and 1,351 controls pooled from two prior studies conducted in King County, Washington. No associations were observed between any of these SNPs and overall risk of prostate cancer, after adjusting for age and multiple comparisons. Risks were not different according to family history of prostate cancer or by smoking (either smoking status or pack-years of smoking) with mostly null associations. With respect to clinical characteristics of prostate cancer, two SNPs in *BRCA2* (rs144848, rs1801406) and two SNP in *ERCC2* (rs1799793, rs13181) showed some associations with Gleason score and tumor stage in single SNP analysis; however ORs were not statistically significantly different between lower and higher Gleason score tumors or between localized versus regional or distant stage tumors.

In relation to *BRCA2* SNPs, although both rs144848 (Asn372His) and rs1801406 (Lys1132 Lys) showed a stronger association with risk of higher grade prostate cancer in Caucasians, the ORs estimates were not statistically significant different from those obtained for Gleason 2–6 or 7(3+4) tumors. However, none of the above SNPs in *BRCA2* were associated with tumor stage in our dataset. The *BRCA2* is considered a strong susceptibility gene in prostate cancer, since studies of families segregating *BRCA2* protein-truncating mutations (35–40), studies of populations who harbor founder mutations such as Icelandic (41) or Ashkenazi Jews (42–44), as well as studies of younger-onset prostate cancer (age at diagnosis < 55 yrs) unselected for family history (45,46) all have reported that men who carry protein-truncating *BRCA2* mutations have increased risk of prostate cancer with relative risk (RRs) ranging from 2.0 to 23.0 depending on several factors including study population, case ascertainment, age at prostate cancer diagnosis and familial history of several cancer such as prostate, breast and ovary. Unlike SNPs, which have an unclear role in protein function, the above deleterious mutations in *BRCA2* result in an earlier truncation of the BRCA2 protein and thus are more likely to be linked to prostate cancer susceptibility; however given their very low prevalence in the general population (~0.1%) it is estimated that <1% of sporadic prostate cancers can be attributed to these disease-associated *BRCA2* mutations (47).

With respect to *ERCC2 (XPD)* SNPs, we found no association with overall risk of prostate cancer; however there was an inverse association between two SNPs: rs1799793 (Asp312Asn) and rs13181 (Lys751Glu) and clinical features of prostate cancer including Gleason score and tumor stage. For both of these two non-synonymous SNPs although men homozygous for the minor allele had a stronger reduction in risk of higher Gleason score or regional or distant tumor stage in comparison to men with the more common genotype, these ORs were not statistically significant for those obtained for low Gleason score (2–6 or 7=3+4) and localized stage prostate cancer. The *ERCC2* gene encodes for a protein that is part of the TFIIH complex, which unwinds the DNA helix around the lesion in the earlier steps of the nucleotide-excision repair (NER) pathway (12). This pathway is responsible for removal of DNA bulky lesions that occur from a variety of exposures, including UV-induced photoproducts, cross-links, oxidative damage or chemical adducts from PAH exposures (48) (11). Two other studies have examined associations between NER pathway and prostate cancer risk (17,21). Hu and colleagues (17) examined associations between NER capacity in isolated prostate tissue as measured in a host-cell reaction assay, and prostate cancer risk is a small clinic-based study of 140 prostate cancer patients and 96 controls. They reported a 2.6-fold increased risk (95%CI 1.2–6.0) of prostate cancer for men in the lowest quartile of NER capacity in comparison to those in the highest quartile (17), however, they did not consider genetic variants in NER pathway genes including *ERCC2*. In another study, Rybicki and colleagues (21) examined associations between the same two variants in *ERCC2* (rs1799793, rs13181) that we evaluated and risk of prostate cancer in a family-based study of 637 cases and 480 brother controls (the study population was primarily Caucasian) and reported a positive association between rs1799793 (Asp312Asn) and prostate cancer, where men with the AA genotype had a 60% increased risk of prostate cancer in comparison to men with the GG or GA genotype (21). No association was observed for *ERCC2* rs13181 in that study (21), nor risks differed by clinical characteristics of prostate cancer We did not observe any association between these two SNPs (rs1799793, rs13181) and risk of prostate cancer in our study; however differences in results could be due several factors including false-positive findings or different study designs i.e. population-based vs. family-based (sibling brothers).

With respect to other SNPs in DNA repair genes we did not find any associations with overall risk of prostate cancer or clinical characteristics of this disease in our study population, although prior studies have reported positive associations between risk of prostate cancer and genetic variants in *OGG1* (19), *XRCC1* (20–24), *MGMT* (22) and *XPC* (25) in different populations. In a small study of 245 cases and 222 controls, Xu and colleagues (19) reported an OR of 3.2

(95% CI 1.19–8.73) for sporadic prostate cancer risk associated with the GG genotype vs. CC genotype for *OGG1* rs1052133 (Ser326Cys). However that SNP was excluded from our analysis due to high frequency of drop-outs. In relation to *XRCC1*, two studies of Caucasian populations (20,21) reported no associations between prostate cancer and rs25487 (Arg399Gln), rs1799782 (Arg194Trp) or rs25489 (Arg280His), which is similar to our findings. However, one of these studies reported effect modification between XRCC1 rs25487 (Arg399Gln) and *ERCC2* rs1799793 (Asp312Asn) in relation to risk of prostate cancer (21). Finally, two small scale studies in Asian populations with a maximum of 250 cases, reported positive associations between risk of prostate cancer and *MGMT* Leu84Phe (22), *XPC* Lys939Gln (25) as well as *XRCC1* Arg194Trp (22)(25). However the allele frequencies of these SNPs in Asians were different from those observed in our study population of Caucasians.

Our study has several strengths and limitations that should be carefully considered when interpreting the results. Strengths of the current study include the population-based design, the sample size, and the availability of information on potential confounding variables, as well as the availability of clinical data on prostate cancer cases. A limitation of our study is that we examined only a small number of SNPs in DNA repair genes with respect to risk of prostate cancer, and some large genes such as *BRCA2* or *MGMT* had minimal coverage. However, the majority of selected tagSNPs in our study were also non-synonomous SNPs with potential functional prediction based on the *in silico* Polyphen program. Another limitation is the small number of African American men in this study that limited the statistical power to examine associations in this group.

Two potential issues that should be considered when pooling datasets of prostate cancer cases with different ascertainment periods are changes in the prevalence of PSA screening as well as a shift of Gleason score reading system over time (49–51). The increase of PSA screening over time would result theoretically in a higher proportion of prostate cancer cases diagnosed with minimal disease in the more recent study (49). To assess this issue, we compared the prevalence of self-reported PSA screening among cases and controls between the two studies. Although the frequency of PSA screening increased among controls from 34% to 58% when comparing study I (1993–1996) and study II (2002–2005), the frequency of PSA screening was similar between prostate cancer cases with different ascertainment periods, 73% and 71%, respectively. In addition the distribution of Gleason score 8 to 10 tumors was similar between the two studies, 9% and 10% respectively, although the prevalence of cases diagnosed with regional or distant stage tumors slightly declined from 26% to 18% when comparing study I (1993–1996) and study II (2002–2005). Another issue is the shift of Gleason score reading over time, with the tendency of pathologists to provide a higher Gleason score for prostate biopsy tumors in the more recent PSA screening era (50,51). Although we did not assess this issue directly, as mentioned before the distribution of Gleason score was similar between the two studies, and the majority of our cases also received radical prostatectomy which usually corrects (either upgrades or downgrades) Gleason scores readings provided from the biopsies. Finally we stratified our data by study ascertainment period and run separate analysis for study I and II, respectively. We didn't find any significant differences in ORs estimates obtained for each study separately, providing further reassurance that data from both studies are comparable.

In conclusion, we found no associations between DNA repair SNPs and overall risk of prostate cancer. Although, two SNPs in *BRCA2* (rs144848, rs1801406) and two SNPs in *ERCC2* (rs1799793, rs13181) showed some associations with Gleason score or tumor stage when comparing homozygous men carrying the minor vs. major allele, results were not statistically significantly different between clinically aggressive and non-aggressive tumors. Although our findings suggest that selected SNPs in DNA repair genes do not contribute to prostate cancer susceptibility, given the complexity of this pathway and its crucial role in maintenance of genomic stability a more comprehensive evaluation of tag SNPs, haplotypes, copy number

variations and pathway-based analyses of all 150 genes in several DNA repair pathways, as well as exploration of gene-environment interactions may be warranted.

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Table 1

Selected characteristics of prostate cancer cases and controls genotyped for SNPs in DNA repair genes, by race

Characteristic	Caucasians			African - Americans		
	Cases (N=1,308)	Controls (N=1,266)	P-value†	Cases (N=149)	Controls (N=85)	P-value†
Age (years); n (%)			0.36			0.0002
35–49	102 (7.8)	107 (8.5)		16 (10.7)	19 (22.4)	
50–54	188 (14.4)	178 (14.1)		26 (17.5)	31 (36.5)	
55–59	325 (24.9)	343 (27.1)		32 (21.5)	15 (17.7)	
60–64	395 (30.2)	334 (26.3)		38 (25.5)	14 (16.5)	
65–69	153 (11.7)	160 (12.6)		24 (16.1)	4 (4.7)	
70–74	145 (11.1)	144 (11.4)		13 (8.7)	2 (2.4)	
First-degree family history of prostate cancer; n (%)			<0.0001			0.04
No	1,025 (78.4)	1,125 (88.9)		119 (79.9)	75 (88.2)	
Yes	283 (21.6)	141 (11.1)		30 (20.1)	10 (11.8)	
Body mass index (BMI), kg/m^2 n (%)			0.34			0.39
< 25.0	429 (32.8)	389 (30.7)		38 (25.5)	21 (24.7)	
25.0–29.9	637 (48.7)	618 (48.8)		69 (46.1)	33 (38.8)	
≥ 30	242 (18.5)	259 (20.5)		42 (28.2)	31 (36.5)	
Smoking status; n (%)			0.13			0.64
Non smoker	522 (39.9)	541 (42.7)		63 (42.3)	31 (36.5)	
Former smoker	631 (48.2)	561 (44.3)		45 (30.2)	30 (35.3)	
Current smoker	155 (11.9)	164 (13.0)		41 (27.5)	24 (28.2)	
Education; n (%)			0.85			0.09
High school or less	230 (17.6)	237 (18.7)		57 (38.3)	24 (28.2)	
Some college	324 (24.8)	300 (23.7)		49 (32.9)	23 (27.1)	

Characteristic	Caucasians			African - Americans		
	Cases (N=1,308)	Controls (N=1,266)	P-value†	Cases (N=149)	Controls (N=85)	P-value†
College degree	369 (28.2)	354 (28.0)		21 (14.1)	21 (24.7)	
Graduate degree	385 (29.4)	375 (29.6)		22 (14.7)	17 (20.0)	
Prostate cancer screening history‡; n (%)			<0.0001			0.002
None	135 (10.3)	168 (13.3)		22 (14.8)	15 (17.7)	
DRE only	223 (17.1)	482 (38.1)		34 (22.8)	36 (42.3)	
PSA	950 (72.6)	616 (48.7)		93 (62.4)	34 (40.0)	
Gleason score, n (%)						
2–4	66 (5.1)			5 (3.4)		
5–6	681 (52.1)			61 (40.9)		
7 (3+4)	355 (27.1)			53 (35.6)		
7 (4+3)	76 (5.8)			14 (9.4)		
8–10	126 (9.6)			14 (9.4)		
Missing	4 (0.3)			2 (1.3)		
Stage of cancer, n (%)						
Localized	1,022 (78.1)			118 (79.2)		
Regional	254 (19.4)			26 (17.5)		
Distant	32 (2.5)			5 (3.4)		
PSA value§ (ng/ml); n (%)			<0.0001			<0.0001
0.01–3.9	178 (13.6)	1,175 (92.8)		11 (7.4)	78 (91.8)	
4.0–9.9	705 (53.9)	74 (5.9)		91 (61.1)	6 (7.1)	
10.0–19.9	188 (14.4)	15 (1.2)		19 (12.8)	1 (1.2)	
≥ 20	118 (9.0)	2 (0.2)		20 (13.4)	-	
Missing	119 (9.1)	-		8 (5.4)	-	

[†] Chi-square p-value;

[‡] Prostate cancer screening history within the 5 years before prostate cancer diagnosis or reference date.

[ξ] Serum PSA value at prostate cancer diagnosis for cases and at interview for controls Abbreviations: DRE - digital rectal examination; PSA - prostate specific antigen.

Table 2

Associations between SNPs in DNA repair genes and prostate cancer risk, by race

Gene	SNP	Genotype	Caucasians							African-American						
			Cases		Controls					Cases		Controls				
			N	%	N	%	OR†	95% CI	Permuted P*	N	%	N	%	OR†	95% CI	Permuted P*
APEX1	rs1320150	AA	424	33.5	415	33.4	1.00	-	0.42	57	40.1	37	46.8	1.00	-	0.84
		AG	612	48.4	615	49.5	0.97	0.82–1.16		65	45.8	33	41.8	1.43	0.77–2.66	
		GG	229	18.1	212	17.1	1.06	0.84–1.33		20	14.1	9	11.4	1.48	0.58–3.79	
		AG + GG	841	66.5	827	66.6	1.00	0.84–1.18		85	59.9	42	53.2	1.44	0.80–2.59	
APEX1	rs2275007	GG	420	33.4	415	33.5	1.00	-	0.79	61	43.0	37	46.8	1.00	-	0.53
		AG	608	48.3	614	49.5	0.98	0.82–1.17		62	43.7	31	39.2	1.40	0.75–2.62	
		AA	230	18.3	211	17.0	1.08	0.85–1.36		19	13.4	11	13.9	1.08	0.44–2.65	
		AG + AA	838	66.6	825	66.5	1.01	0.85–1.19		81	57.0	42	53.2	1.32	0.73–2.36	
BRCA2	rs144848	TT	655	51.6	654	52.6	1.00	-	0.52	104	73.2	59	74.7	1.00	-	0.36
		GT	498	39.4	500	40.2	0.99	0.84–1.17		36	25.4	18	22.8	0.98	0.49–1.95	
		GG	116	9.1	89	7.2	1.30	0.98–1.75		2	1.4	2	2.5	0.48	0.06–3.85	
		GT + GG	614	48.5	589	47.4	1.04	0.89–1.22		38	26.8	20	25.3	0.93	0.48–1.81	
BRCA2	rs15869	AA	770	60.8	787	63.3	1.00	-	0.59	136	95.1	71	89.9	1.00	-	0.90
		AC	439	34.7	398	32.0	1.13	0.95–1.33		7	4.9	7	8.9	0.62	0.20–1.91	
		CC	57	4.5	59	4.7	0.99	0.68–1.44		-	-	1	1.3	-	-	
		AC + CC	496	39.2	457	36.7	1.11	0.94–1.30		7	4.9	8	10.1	0.53	0.18–1.58	
BRCA2	rs1801406	AA	635	50.5	563	45.2	1.00	-	0.22	79	54.5	46	58.3	1.00	-	0.53
		AG	501	39.9	556	44.6	**0.80**	**0.68–0.94**		58	40.0	31	39.2	1.13	0.62–2.06	
		GG	121	9.6	127	10.2	0.84	0.64–1.11		8	5.5	2	2.5	3.34	0.65–17.12	
		AG + GG	622	49.5	683	54.8	**0.81**	**0.69–0.95**		66	45.5	33	41.7	1.25	0.70–2.25	

Gene	SNP	Genotype	Caucasians							African-American						
			Cases		Controls					Cases		Controls				
			N	%	N	%	OR†	95% CI	Permuted P*	N	%	N	%	OR†	95% CI	Permuted P*
BRCA2	rs543304	TT	821	65.1	839	67.6	1.00	-	0.65	98	68.5	44	55.7	1.00	-	0.72
		CT	399	31.6	364	29.3	1.12	0.94–1.33		42	29.4	30	38.0	0.59	0.32–1.10	
		CC	41	3.3	38	3.1	1.11	0.70–1.74		3	2.1	5	6.3	0.27	0.06–1.21	
		CT + CC	440	34.9	402	32.4	1.12	0.95–1.32		45	31.5	35	44.3	**0.54**	**0.30–0.99**	
ERCC2 (XPD)	rs1052555	CC	591	46.9	565	45.4	1.00	-	0.47	110	76.4	60	76.0	1.00	-	0.31
		CT	549	43.6	535	43.0	0.98	0.83–1.16		29	20.1	17	21.5	0.82	0.40–1.68	
		TT	119	9.5	144	11.6	0.79	0.60–1.03		5	3.5	2	2.5	1.56	0.27–8.86	
		CT + TT	668	53.1	679	54.6	0.94	0.80–1.10		34	23.6	19	24.0	0.90	0.45–1.76	
ERCC2 (XPD)	rs13181	TT	505	41.0	480	39.1	1.00	-	0.17	87	59.6	50	60.2	1.00	-	0.41
		GT	575	46.6	571	46.5	0.96	0.81–1.13		48	32.9	28	33.7	0.85	0.46–1.57	
		GG	153	12.4	177	14.4	0.82	0.64–1.05		11	7.5	5	6.0	1.19	0.37–3.78	
		GT + GG	728	59.0	748	60.9	0.92	0.79–1.09		59	40.4	33	39.7	0.90	0.50–1.61	
ERCC2 (XPD)	rs1799793	GG	545	44.0	527	43.2	1.00	-	0.08	106	73.6	65	79.3	1.00	-	0.77
		AG	575	46.4	528	43.2	1.05	0.89–1.25		31	21.5	15	18.3	1.28	0.62–2.64	
		AA	120	9.7	166	13.6	**0.70**	**0.54–0.91**		7	4.9	2	2.4	2.35	0.44–12.43	
		AG + AA	695	56.1	694	56.8	0.97	0.83–1.13		38	26.4	17	20.7	1.40	0.71–2.77	
ERCC2 (XPD)	rs238406	GG	365	29.0	383	30.9	1.00	-	0.24	112	77.8	65	80.2	1.00	-	0.14
		GT	636	50.4	600	48.5	1.11	0.93–1.33		29	20.1	16	19.8	0.98	0.48–2.00	
		TT	260	20.6	255	20.6	1.07	0.86–1.34		3	2.1	0	0.0	-	-	
		GT + TT	896	71.1	855	69.1	1.10	0.93–1.31		32	22.2	16	19.8	1.09	0.54–2.20	
ERCC4 (XPF)	rs1799801	TT	633	50.3	623	50.1	1.00	-	0.91	96	66.2	55	69.6	1.00	-	0.72
		CT	521	41.4	521	41.9	0.98	0.84–1.16		46	31.7	23	29.1	1.27	0.67–2.40	
		CC	105	8.3	99	8.0	1.04	0.78–1.40		3	2.1	1	1.3	3.02	0.29–30.9	

Gene	SNP	Genotype	Caucasians							African-American						
			Cases		Controls					Cases		Controls				
			N	%	N	%	OR†	95% CI	Permuted P*	N	%	N	%	OR†	95% CI	Permuted P*
		CT + CC	626	49.7	620	49.9	0.99	0.85–1.16		49	33.8	24	30.4	1.33	0.71–2.49	
ERCC4 (XPF)	rs1800067	GG	1025	84.0	1012	83.0	1.00	-	0.79	136	94.4	78	96.3	1.00	-	0.59
		AG	183	15.0	202	16.6	0.89	0.72–1.11		8	5.6	3	3.7	2.12	0.52–8.54	
		AA	13	1.1	5	0.4	2.58	0.92–7.25		-	-	-	-	-	-	
		AG + AA	196	16.1	207	17.0	0.93	0.75–1.16								
MGMT	rs12917	CC	949	75.9	916	74.1	1.00	-	0.87	106	72.1	60	74.1	1.00	-	0.68
		CT	269	21.5	298	24.1	0.87	0.72–1.05		35	23.8	20	24.7	1.18	0.61–2.29	
		TT	32	2.6	23	1.9	1.34	0.78–2.31		6	4.1	1	1.2	2.75	0.30–25.41	
		CT + TT	301	24.1	321	26.0	0.91	0.75–1.09		41	27.9	21	25.9	1.26	0.66–2.40	
MGMT	rs2308321	AA	926	76.7	922	77.2	1.00	-	0.50	130	92.9	73	91.3	1.00	-	0.39
		AG	267	22.1	256	21.4	1.04	0.86–1.26		10	7.1	7	8.8	0.82	0.29–2.32	
		GG	14	1.2	17	1.4	0.82	0.40–1.67		-	-	-	-	-	-	
		AG + GG	281	23.3	273	22.8	1.02	0.85–1.24								
MGMT	rs2308327	AA	950	76.1	960	77.1	1.00	-	0.75	134	92.4	75	90.4	1.00	-	0.31
		AG	276	22.1	266	21.4	1.05	0.87–1.27		11	7.6	8	9.6	0.74	0.27–2.00	
		GG	22	1.8	20	1.6	1.11	0.60–2.05		-	-	-	-	-	-	
		AG + GG	298	23.9	286	23.0	1.05	0.87–1.26								
MUTYH	rs3219484	GG	1085	86.4	1070	85.7	1.00	-	0.77	140	97.9	75	94.9	1.00	-	0.77
		AG	164	13.1	173	13.9	0.94	0.74–1.18		3	2.1	4	5.1	0.29	0.06–1.36	
		AA	7	0.6	5	0.4	1.39	0.44–4.41		-	-	-	-	-	-	
		AG + AA	171	13.6	178	14.3	0.95	0.76–1.19								
MUTYH	rs9429072	AA	720	57.1	686	55.0	1.00	-	0.37	34	23.5	24	30.4	1.00	-	0.54

Gene	SNP	Genotype	Caucasians							African-American						
			Cases		Controls					Cases		Controls				
			N	%	N	%	OR†	95% CI	Permuted P*	N	%	N	%	OR†	95% CI	Permuted P*
		AG	455	36.1	485	38.9	0.89	0.76–1.05		71	49.0	32	40.5	1.39	0.69–2.79	
		GG	85	6.8	76	6.1	1.07	0.77–1.48		40	27.6	23	29.1	1.11	0.51–2.39	
		AG + GG	540	42.9	561	45.0	0.92	0.78–1.07		111	76.6	55	69.6	1.27	0.67–2.42	
OGG1	rs3218997	CC	1126	91.4	1137	91.5	1.00	-	0.84	139	95.9	77	97.5	1.00	-	0.52
		CT	106	8.6	106	8.5	1.01	0.76–1.34		6	4.1	2	2.5	1.82	0.34–9.78	
XPC	rs1126547	CC	969	76.8	938	75.4	1.00	-	0.33	109	75.7	61	77.2	1.00	-	0.53
		CG	273	21.6	287	23.1	0.92	0.76–1.11		30	20.8	17	21.5	0.93	0.46–1.89	
		GG	20	1.6	19	1.5	1.01	0.54–1.91		5	3.5	1	1.3	1.92	0.21–17.34	
		CG + GG	293	23.2	306	24.6	0.93	0.77–1.11		35	24.3	18	22.8	0.99	0.50–1.97	
XPC	rs2228001	AA	457	36.4	461	36.9	1.00	-	0.66	70	47.6	36	43.4	1.00	-	0.23
		AC	595	47.3	600	48.0	1.00	0.84–1.19		61	41.5	38	45.8	0.80	0.44–1.46	
		CC	205	16.3	190	15.2	1.09	0.86–1.38		16	10.9	9	10.8	1.04	0.40–2.69	
		AC + CC	800	63.6	790	63.2	1.02	0.87–1.20		77	52.4	47	56.6	0.85	0.48–1.49	
XPC	rs2733532	CC	461	36.5	467	37.6	1.00	-	0.74	72	50.0	39	47.6	1.00	-	0.41
		CT	602	47.7	599	48.2	1.02	0.86–1.21		57	39.6	35	42.7	0.91	0.50–1.65	
		TT	199	15.8	176	14.2	1.14	0.90–1.46		15	10.4	8	9.8	1.19	0.45–3.20	
		CT + TT	801	63.5	775	62.4	1.05	0.89–1.23		72	50.0	43	52.4	0.96	0.54–1.69	
XPC	rs2733534	GG	340	27.6	311	25.4	1.00	-	0.39	58	40.0	39	47.6	1.00	-	0.66
		CG	607	49.2	635	51.8	0.88	0.72–1.06		64	44.1	35	42.7	1.24	0.67–2.28	
		CC	286	23.2	279	22.8	0.94	0.75–1.18		23	15.9	8	9.8	1.88	0.74–4.79	
		CG + CC	893	72.4	914	74.6	0.90	0.75–1.07		87	60.0	43	52.4	1.36	0.77–2.42	
XPC	rs8516	TT	771	61.1	753	60.3	1.00	-	0.85	106	73.6	66	83.5	1.00	-	0.76

Gene	SNP	Genotype	Caucasians							African-American						
			Cases		Controls					Cases		Controls				
			N	%	N	%	OR†	95% CI	Permuted P*	N	%	N	%	OR†	95% CI	Permuted P*
		CT	425	33.7	436	34.9	0.95	0.81–1.13		38	26.4	13	16.5	1.73	0.83–3.60	
		CC	66	5.2	60	4.8	1.08	0.75–1.55		-	-	-	-	-	-	
		CT + CC	491	38.9	496	39.7	0.97	0.83–1.14								
XRCC1	rs1799782	CC	1098	88.1	1071	86.7	1.00	-	0.23	131	89.7	72	86.8	1.00	-	0.60
		CT	143	11.5	158	12.8	0.88	0.69–1.12		15	10.3	9	10.8	0.97	0.38–2.46	
		TT	5	0.4	6	0.5	0.82	0.25–2.68		-	-	2	2.4	-	-	
		CT + TT	148	11.9	164	13.3	0.88	0.69–1.11		15	10.3	11	13.2	0.77	0.32–1.86	
XRCC1	rs25487	GG	522	41.5	481	38.8	1.00	-	0.77	103	71.5	53	64.6	1.00	-	0.83
		AG	576	45.8	590	47.6	0.90	0.76–1.07		37	25.7	27	33.0	0.67	0.36–1.25	
		AA	159	12.7	169	13.6	0.87	0.68–1.11		4	2.8	2	2.4	0.97	0.16–5.84	
		AG + AA	735	58.5	759	61.2	0.89	0.76–1.05		41	28.5	29	35.4	0.69	0.38–1.27	
XRCC1	rs25489	GG	1120	90.0	1145	91.4	1.00	-	0.26	137	93.8	76	91.6	1.00	-	0.61
		AG	121	9.7	106	8.5	1.17	0.87–1.53		9	6.2	7	8.4	0.59	0.20–1.76	
		AA	3	0.2	2	0.2	1.55	0.26–9.27		-	-	-	-	-	-	
		AG + AA	124	10.0	108	8.6	1.17	0.89–1.54								
XRCC1	rs2854509	CC	798	63.4	777	62.8	1.00	-	0.66	98	67.6	56	70.0	1.00	-	0.21
		AC	406	32.3	400	32.3	0.99	0.83–1.17		39	26.9	23	28.8	1.09	0.57–2.08	
		AA	55	4.4	61	4.9	0.88	0.60–1.28		8	5.5	1	1.3	2.94	0.34–25.66	
		AC + AA	461	36.6	461	37.2	0.97	0.83–1.14		47	32.4	24	30.0	1.19	0.64–2.21	
XRCC1	rs915927	AA	400	31.8	409	32.8	1.00	-	0.73	62	42.8	30	38.0	1.00	-	0.41
		AG	622	49.4	618	49.6	1.03	0.86–1.23		54	37.2	38	48.1	0.79	0.42–1.50	
		GG	238	18.9	220	17.6	1.11	0.88–1.39		29	20.0	11	13.9	1.32	0.56–3.11	

Gene	SNP	Genotype	Caucasians							African-American						
			Cases		Controls					Cases		Controls				
			N	%	N	%	OR†	95% CI	Permuted P*	N	%	N	%	OR†	95% CI	Permuted P*
		AG + GG	860	68.3	838	67.2	1.05	0.89–1.24		83	57.2	49	62.0	0.92	0.51–1.65	

Total number of cases and controls in both Caucasians and African-Americans vary by SNPs due to missing genotype data.

†ORs and 95% CI are adjusted for age at diagnosis (cases) and age at reference date (controls).

*Permuted *P*-values are for the co-dominant models (2 degrees of freedom) and present the adjusted *P*-values for multiple comparisons using a permutation procedure (see statistical methods for details).

Table 3

Associations between SNPs in DNA repair genes and clinical features of prostate cancer among Caucasians

Gleason Score			Controls		Cases*: Gleason score 2–6 or 7 (3+4)				Cases*: Gleason score 7 (4+3) or 8–10				
Gene	**SNP**	**Genotype**	**N**	**%**	**N**	**%**	**OR_1†**	**95% CI**	**N**	**%**	**OR_2†**	**95% CI**	**p-value $OR_1 \neq OR_2$**
BRCA2	rs144848	TT	654	52.6	562	52.5	1.00	-	92	47.2	1.00	-	
		GT	500	40.2	416	38.9	0.99	0.83–1.18	81	41.5	1.16	0.84–1.60	0.34
		GG	89	7.2	92	8.6	1.32	0.95–1.83	22	11.3	1.83	1.09–3.08	0.22
BRCA2	rs1801406	AA	563	45.2	534	50.4	1.00	-	98	50.5	1.00	-	
		AG	556	44.6	415	39.2	0.75	0.63–0.90	85	43.8	0.86	0.63–1.18	0.42
		GG	127	10.2	110	10.4	0.87	0.65–1.17	11	5.7	0.48	0.25–0.93	0.08
ERCC2	rs13181	TT	480	39.1	418	40.4	1.00	-	84	43.5	1.00	-	
		GT	571	46.5	492	47.5	0.96	0.80–1.15	82	42.5	0.80	0.57–1.11	0.28
		GG	177	14.4	126	12.2	0.75	0.57–0.99	27	14.0	0.80	0.50–1.28	0.81
ERCC2	rs1799793	GG	527	43.2	450	43.1	1.00	-	92	47.7	1.00	-	
		AG	528	43.2	490	47.0	1.06	0.88–1.27	84	43.5	0.88	0.64–1.21	0.26
		AA	166	13.6	103	9.9	0.67	0.50–0.89	17	8.8	0.54	0.31–0.93	0.45

Tumor Stage			Controls		Cases*: Localized Stage				Cases*: Regional/Distant Stage				
Gene	**SNP**	**Genotype**	**N**	**%**	**N**	**%**	**OR_1†**	**95% CI**	**N**	**%**	**OR_2†**	**95% CI**	**p-value $OR_1 \neq OR_2$**
BRCA2	rs144848	TT	654	52.6	512	51.6	1.00	-	143	51.8	1.00	-	
		GT	500	40.2	393	39.6	1.02	0.85–1.23	105	38.0	1.00	0.75–1.32	0.85
		GG	89	7.2	88	8.9	1.37	0.99–1.90	28	10.1	1.57	0.98–2.51	0.57
BRCA2	rs1801406	AA	563	45.2	495	50.5	1.00	-	140	50.5	1.00	-	
		AG	556	44.6	389	39.7	0.76	0.64–0.92	112	40.4	0.79	0.60–1.04	0.84

Tumor Stage			Controls		Cases*: Localized Stage				Cases*: Regional/Distant Stage				p-value $OR_1 \neq OR_2$
Gene	**SNP**	**Genotype**	**N**	**%**	**N**	**%**	**OR_1†**	**95% CI**	**N**	**%**	**OR_2†**	**95% CI**	
		GG	127	10.2	96	9.8	0.81	0.60–1.10	25	9.1	0.79	0.49–1.26	0.89
ERCC2	rs13181	TT	480	39.1	389	40.4	1.00	-	116	43.1	1.00	-	
		GT	571	46.5	450	46.7	0.94	0.78–1.14	125	46.5	0.89	0.67–1.19	0.74
		GG	177	14.4	125	13.0	0.79	0.60–1.04	28	10.4	0.63	0.40–0.99	0.33
ERCC2	rs1799793	GG	527	43.2	422	43.5	1.00	-	123	45.6	1.00	-	
		AG	528	43.2	448	46.2	1.02	0.85–1.23	127	47.0	1.03	0.78–1.36	0.96
		AA	166	13.6	100	10.3	0.68	0.51–0.91	20	7.4	0.50	0.30–0.83	0.24

*Total number of cases and controls vary by SNPs due to missing genotype data. Cases with missing data on Gleason score (n=6) were excluded from respective analyses.

†ORs and 95% CI are adjusted for age and prostate cancer screening history within the 5 years before prostate cancer diagnosis or reference date.