Published in final edited form as:
Methods Mol Biol. 2009 ; 471: 361–385. doi:10.1007/978-1-59745-416-2_18.

Single nucleotide polymorphisms in DNA repair genes and prostate cancer risk

Jong Park[1,*], **Yifan Huang**[1], and **Thomas A. Sellers**[1]

[1]Division of Cancer Prevention and Control, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL.

Abstract

The specific causes of prostate cancer are not known. However, multiple etiological factors, including genetic profile, metabolism of steroid hormones, nutrition, chronic inflammation, family history of prostate cancer, and environmental exposures are thought to play significant roles. Variations in exposure to these risk factors may explain inter-individual differences in prostate cancer risk. However, regardless of the precise mechanism(s), a robust DNA repair capacity may mitigate any risks conferred by mutations from these risk factors. Numerous single nucleotide polymorphisms (SNPs) in DNA repair genes have been found, and studies of these SNPs and prostate cancer risk are critical to understanding the response of prostate cells to DNA damage. A few SNPs in DNA repair genes cause significantly increased risk of prostate cancer, however, in most cases, the effects are moderate and often depend upon interactions among the risk alleles of several genes in a pathway or with other environmental risk factors. This report reviews the published epidemiologic literature on the association of SNPs in genes involved in DNA repair pathways and prostate cancer risk.

Keywords

Prostate cancer; polymorphism; DNA repair; cancer susceptibility

INTRODUCTION

Prostate is the most common site of cancer and the third leading cause of cancer mortality in men in the United States [1]. There is a large variation in prostate cancer incidence rates among ethnic groups. Incidence rates are the highest among African Americans (272 per 100,000 per year) and the lowest among Asians (2 per 100,000 per year) [1, 2]. Incidence of prostate cancer is increasing steadily in almost all countries, and the lifetime risk of prostate cancer for men in the United States is 18% [1, 3].

Although the specific causes of prostate cancer are not known, androgens, estrogens, inflammation and DNA repair capacity have been implicated. Androgens which play an important part in development and maintenance of the prostate can induce prostate cancer in rodents [4], and stimulate the *in vitro* proliferation of prostate cancer cells [5]. Carcinogenesis in prostate tissue involves multiple genetic events.

DNA is constantly damaged by endogenous oxygen free radicals and exogenous chemicals. DNA mutations are estimated to spontaneously occur 20,000–40,000 times everyday [6, 7].

[*]**Corresponding author:** Jong Park, Ph. D., H. Lee Moffitt Cancer Center and Research Institute, University of South Florida, MRC3047A, 12902 Magnolia Drive, Tampa, FL 33612; Tel: (813) 745-1703; Fax: (813) 745-1720; jong.park@moffitt.org.

The DNA repair process is important to the survival of the cell, therefore, different repair pathways are available to reverse the different types of DNA damage. In fact, over 150 DNA repair enzymes participate in this process [8]. Defects in these DNA repair pathways may increase persistent mutations in daughter cell generations, genomic instability, and ultimately a prostate cancer risk. These DNA repair genes can be classified into several distinct pathways: Direct reversal, base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), and double-strand break repair (DSBR). Depending upon the DNA damaging agents, different levels of contribution from different classes of DNA repair enzymes could be expected.

In this manuscript, we focused on single nucleotide polymorphisms (SNPs) and phenotypes in DNA repair genes that have been investigated in published epidemiological studies of prostate cancer.

METHODS

Numerous SNPs in different DNA repair genes have been identified, and many of them have been investigated in relation to human cancer susceptibility [9]. We identified studies relevant to prostate cancer using the search engine, Pubmed, (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi) in October 2007. The inclusion criteria for this manuscript were epidemiological studies of the association between polymorphisms in DNA repair genes and prostate cancer risk. Among 40 studies obtained from the search phrases "DNA repair" AND “prostate cancer" AND “polymorphism”, 11 epidemiological studies were included after review of the articles [10–20]. Among twelve additional epidemiological studies which were obtained after searching by single DNA repair gene name AND “prostate cancer”, five studies were excluded because they reported associations between phenotypes, such as expressions or activities of DNA enzymes and prostate cancer risk [21–25]. The remaining six studies also were included in this manuscript [26–31]. One article [19] was excluded from this review because the data of this article appears to be redundant with one published in Asian Journal of Andrology [31], thus a total of 16 published studies form the basis of this review.

The following notation is used to describe SNPs: uppercase letters represent amino acids with numbers indicating the codon and lowercase letters represent nucleotides with numbers indicating the sequence position.

RESULTS

By the end of October 2007, associations between SNPs in DNA repair genes and risk of prostate cancer have been reported in 16 published studies. Table 1 provides details on case-control studies of DNA repair gene polymorphisms and levels of association. Most studies were conducted in North America and five studies were conducted in China [12, 31], Taiwan [20], Japan [10], and UK [30]. Six studies were relatively large (438 – 996 cases) [13, 17, 18, 26, 28, 30], but Ten studies included 250 or fewer cases. Ten studies were hospital based case-control studies and four studies were population-based studies [12, 15, 27, 30]. Two studies used sibling and family based designs [13, 18].

Table 2 displays the SNPs in DNA repair genes included in this chapter with allele frequencies, SNP identification number and their potential functional effects.

1. Base excision repair (BER) pathway

Base excision repair pathway targets DNA damaged during replication or by environmental agents. Repair of DNA mutations is necessary so that sequence errors are not transmitted to

daughter cells. The single damaged base in DNA caused by endogenous metabolism or environmental oxidizing agents result in DNA adducts. This damage has been proposed to play a critical role in carcinogenesis in prostate tissue. Base excision repair involves removing the mutated base out of the DNA and repairing the base alone (Figure 1A).

Repair of a mutated base is primarily conducted by enzymes involved in BER with apurinic/apyrimidic (A/P) endonuclease (APE1), human 8-oxoguanine DNA glycosylase (hOGG1), DNA ligase, DNA polymerase delta (POLD1), X-ray repair cross-complementing group 1 (XRCC1), and poly (ADP-ribose) polymerase (ADPRT) [32–34].

1.a. human 8-oxoguanine DNA glycosylase (hOGG1)—The enzyme hOGG1 catalyzes the excision and removal of single base adducts [35, 36]. Base excision repair by hOGG1 enzyme leaves a single nucleotide space. This space is filled by DNA polymerase b, and the nick is sealed by the DNA ligase III/XRCC1 complex, which acts as a scaffold for interaction with other BER enzymes [37]. It is expressed as twelve alternatively-spliced isoforms with only the 1α-form containing a nuclear translocation signal [38]. Relatively high levels of expression of hOGG1 have been shown in several human tissues, including prostate [14, 21]. Public database (http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=4968) lists 10 SNPs at the *hOGG1* locus [39]. *hOGG1* codon 326 polymorphism (rs1052123) in the 1α-specific exon 7 of the *hOGG1* results in an amino acid substitution from serine to cysteine (Table 1). Results of studies for functional impact of the *hOGG1* S326C polymorphism are inconsistent (Table 2). These studies used different measuring methods, HPLC, flow cytometry, and different specimens, such as cell lines, leukocytes, and tissues. No difference in catalytic activities was observed between the *hOGG1* 326C and *hOGG1* 326S alleles in several studies [40–46]. However, the *hOGG1* encoded by the wild-type 326S allele exhibited higher DNA repair activity than the *hOGG1* 326C variant in other studies [38, 47–50].

The role of *hOGG1* 326 polymorphism in susceptibility to prostate cancer was assessed in four studies conducted in the US and Canada [14, 16, 18, 26]. The first was a population and family-based study that identified a significantly *decreased* risk associated with the *hOGG1* 326CC genotype [16]. This association was significant in non-familial prostate cancer patients, but not for familial prostate cancer. In contrast, the second, hospital-based study observed a positive relationship with prostate cancer risk [14]. The other two larger studies (996 and 439 cases) found no association between *hOGG1* S326C polymorphism and prostate cancer risk [18, 26]. These inconsistent results could be explained by small sample sizes of first two studies (n=84 and 245 cases). Epidemiological studies of the *hOGG1* S326C polymorphism with risk of other cancers show consistent evidence for an increased risk for esophageal [51], lung [52–59], nasopharyngeal [60], upper aero-digestive tract [60–62] and colon [63] cancers.

Xu *et al.* (2002) investigated other *hOGG1* polymorphisms in addition to codon 326 polymorphism. Among 9 polymorphisms investigated in the *hOGG1* promoter region, significantly increased risks were observed for homozygous polymorphic genotypes of two variants as compared with wild types (*hOGG1* a7143g and a11657g) [16]. A larger study (n=996 cases) did not replicate the *hOGG1* a11657g finding [26]. The difference of these two studies is sample sizes. The first study observed a significant result based upon 1 control and 11 patients with homozygous *hOGG1* 11657gg genotype.

1.b. X-ray repair cross-complementing group 1 (XRCC1)—After base excision by hOGG1 enzyme, the XRCC1/DNA ligase III complex seals the space [37]. Although 32 SNPs in *XRCC1* have been reported [39], only three SNPs have been investigated as potential prostate cancer risk factors [R194W (rs17997820), R280H (rs25489) and R399Q

(rs25487)]. The functional significance of the *XRCC1* 194W allele is somewhat controversial. One study reported lower bleomycin and benzo(a)pyrene diol epoxide sensitivity *in vitro* [64], but these results were not confirmed by other investigators [65–68] (Table 2). However, the *XRCC1 R*194W polymorphism may have detectable effect on DNA-adduct levels, mutation rates, or sensitivity to ionizing radiation [66, 67, 69, 70]. The functional significance of codon R280H polymorphism is not yet well-established; however, the codon 280 amino acid is located in the proliferating cell nuclear antigen binding region which has been associated with higher bleomycin sensitivity [71, 72]. The *XRCC1* 399Q allele has been associated with higher levels of aflatoxin B1-DNA adducts and higher bleomycin sensitivity [64, 69, 70].

Consistent with the functional data, the *XRCC1* R194W does not appear to influence risk in two small studies (n=76 and 165 cases) [10, 15]. However, a recent study suggested 194W allele provides a protective effect [31]. The *XRCC1* R280H polymorphism which has been evaluated in two small studies, can not reach any conclusion on effect with prostate cancer [15, 31].

The *XRCC1* R399Q polymorphism has been the most frequently investigated of the BER genes. Recently, Chen *et al.* (2006) reported a significant association between *XRCC1* R399Q polymorphism and prostate cancer risk among Caucasians, but not in African Americans [11]. Two studies in China observed a significantly increased risk with the *XRCC1* R399*Q* polymorphism [12, 31]. The largest study to date [13] and three smaller studies [10, 15, 27] did not replicate the positive association. However, two small studies reported a significantly higher risk among men with the *XRCC1* 399 QQ genotype and low vitamin E intake/antioxidants [15, 27].

In summary, the *XRCC1* R399Q polymorphism has been associated with risk in 5 of 7 studies, but only among men with low antioxidant, vitamin intake in two of five studies. Additional studies are needed to clarify these potential associations.

1.c. Apurinic/apyrimidic (A/P) endonuclease (APE1)—When BER enzymes initiate repair, the phosphodiester bond at the 5’ side of the intact apurinic/apyrimidinic site is incised by APE1, which is the rate-limiting enzyme. Six polymorphisms in *APE1* have been reported, including relatively common alleles at codons Q51H (rs1048945) and D148E (rs3136820) [39]. Although the functional significance of *APE1* 51H allele has not been reported, it is conserved in most mammals and located in the *Ref1* domain, which is essential for redox regulation of DNA binding proteins, such as p53 [73]. Therefore, *APE1* Q51H polymorphism may affect the ability of APE1 to regulate DNA binding activity. The *APE1* D148E polymorphism is associated with mitotic delay of lymphocytes from healthy subjects, implying higher sensitivity to ionizing radiation [66]. However, this variant was predicted as no impact on endonuclease and DNA binding activity in *in vitro* functional analysis [73],[74].

Both *APE1* Q51H and D148E polymorphisms have been examined in a hospital based study of Caucasians and African Americans. No associations between these polymorphisms and prostate cancer risk were observed [11].

1.d. Poly (ADP-ribose) polymerase (ADPRT)—ADPRT is involved in DNA-damage signaling, genomic stability of damaged cells, BER, recombination and the transcriptional regulation of tumor suppressor genes [75, 76]. ADPRT recognizes and binds DNA damage, recruits other DNA-repair enzymes to the site of damage, and provides support for ligation [77]. Twenty-five polymorphisms in *ADPRT* have been reported, including the relatively common *ADPRT* V762A (rs1136410) [39].

The change from valine to alanine moves the codon 762 residue further away from the codon 888G residue, which is a part of the active site [77]. Locket *et al.* (2004) observed that *ADPRT* V762A is significantly associated with prostate cancer risk and decreased enzyme function in response to oxidative damage [28].

2. Nucleotide excision repair (NER) pathway

NER is associated with the repair of bulky adducts [78, 79] induced by several suspected environmental prostate cancer carcinogens, such as PAHs, heterocyclic aromatic amines from well-done meats, and pesticides. The NER pathway is a complex biochemical process that requires 20–25 enzymes and at least four steps: (*a*) damage recognition by a complex of bound proteins including xeroderma pigmentosum complementation group C *(*XPC*)*, XPA, and replication protein A (RPA); (*b*) unwinding of the DNA by the transcription factor IIH (TFIIH) complex that includes XPD(ERCC2); (*c*) removal of the damaged single-stranded fragment (usually about 27–30 bp) by molecules including an ERCC1 and XPF complex and XPG; and (*d*) synthesis by DNA polymerases [6](Figure 1B).

2.a. Xeroderma pigmentosum complementation group D *(*XPD*)*—The *XPD* (*ERCC2*) gene product is a subunit of TFIIH (DNA helicase), promotes bubble formation, and is necessary for NER and transcription. Fourteen polymorphisms in *XPD* have been reported [39], including common alleles at codons D312N (rs1799793) and K751Q (rs1052559). Several studies reported that subjects with wild-type genotypes for *XPD* K751Q and D312N polymorphisms exhibit the highest NER activity, while homozygous variant genotypes of either polymorphism show low NER activity [80, 81]. Hou *et al.* (2002) reported that the *XPD* 312N allele have reduced capacity to repair aromatic DNA adducts [82, 83]. Lunn *et al.* (2000) reported that *XPD* K751Q was associated with higher levels of chromatid aberrations in white blood cells [84]. Conversely, Duell *et al.* (2000) [85] evaluated phenotypic effects of codons 312 and 751 polymorphisms by measuring two markers of DNA damage, sister chromatid exchange (SCE) frequencies and polyphenol DNA adducts. Both polymorphisms were unrelated to SCE frequency or DNA adduct level [85].

A potential role of *XPD* codons D312N and K751Q with prostate cancer risk has been investigated in four studies [12, 13, 17, 20]. All four studies observed no association between *XPD* K751Q polymorphism and prostate cancer risk in US, Taiwanese and Chinese populations. Rybicki *et al*. (2004) [13] and Bau et al. (2007) [20] observed a significant risk increase with the D312N polymorphism. However, this was not replicated by Lockett et al. [17] after adjustment for age, BPH, family history and smoking. Bau et al. (2007) reported that no a significant difference in the frequency of the XPD promoter -114 polymorphism between cases and controls

2.b. Xeroderma pigmentosum complementation group F *(*XPF*)*/(ERCC4)—XPF is a key enzyme responsible for excising bulky adducts from damaged DNA. XPF interacts with the ERCC1 together to form a complex which is required to repair DNA interstrand cross-linking damage [86]. Ten polymorphisms in *XPF* have been reported, [39] but only R415Q (rs1800067) has been studied in an epidemiological investigation. Lockett *et al.* (2005) reported that *XPF* R415Q polymorphism was associated with a moderate, near significant increase in prostate cancer risk (OR=1.4) [17].

2.c. Xeroderma pigmentosum complementation group G *(*XPG*)*/ (ERCC5)—XPG is responsible for a structure-specific endonuclease activity that is essential for the two incision steps in NER [86]. The XPG enzyme has been suggested to act on the single-stranded region created as a result of the combined action of the XPB helicase and the XPD

helicase at the DNA damage site. XPG incises the 3' side of damaged DNA before the 5' incision made by XPF-ERCC1 complexes. XPG has a structural function in the complex of the DNA-hR23B. Twelve SNPs were reported including *XPG* D1104H (rs17655) [39]. The functional effects of D1104H SNP are still unknown, but the lack of association with prostate cancer risk [17] decreases the incentives to pursue small studies.

2.d. Xeroderma pigmentosum complementation group C *(*XPC*)*—In the early steps of the NER process, the XPC-hR23B protein complex has a structure-specific affinity for certain defined lesions. Thus, this complex can bind damaged DNA and change the DNA conformation around the lesion. DNA damage recognition is carried out by the XPC-hR23B protein complex [87], followed by recruitment of the transcription factor IIH (TFIIH) complex. Among twenty known SNPs [39], two common polymorphisms at codons A499V (rs2228000) and K939Q (rs2228001) have been investigated. There are no published data on their potential functional significance. Lockett *et al.* (2005) observed no significant association between these polymorphisms and prostate cancer risk [17]. However, a small study (n=165 cases) observed a significant 2.5 fold risk increase among Japanese men with the 939K allele [10].

2.e. human homolog RAD23B (hR23B)—The hR23B enzyme, which is the human homolog of the yeast NER protein RAD23, forms a complex with XPC. The XPC-hR23B-TFIIH complex unwinds the DNA duplex around the damaged site. Five SNPs have been reported [39], but only the A249V has been investigated. Lockett *et al.* (2005) found no association between this SNP and prostate cancer risk [17], and the absence of functional data tempers interest.

3. Double-strand break repair pathway

Double-strand breaks are produced by replication failure or by DNA damaging agents such as ionizing radiation. Two repair pathways exist to repair double strand breaks: (a) the homologous recombination repair relies on DNA sequence complementarity between the intact chromatid and the damaged chromatid as the bases of stand exchange and repair (Figure 1C); (b) the non-homologous end-joining repair pathway requires direct DNA joining of the two double-strand-break ends [88] (Figure 1D).

3.a. Xeroderma pigmentosum complementation group 3 (XRCC3)—XRCC3 is involved in homologous recombination repair process and at least 6 SNPs have been identified [39]. *Araujo et al.* (2002) reported that the variant XRCC3 enzyme (T241M) was functionally active for homology-directed repair (HDR) determined by a quantitative fluorescence assay. They also found that cells expressing this variant have been found to be no more sensitive to DNA damaging agents than cells expressing the wild-type enzyme [89].

XRCC3 T241M polymorphism has been analyzed in relation to prostate cancer risk in a population-based study in China [12]. This relatively small study detected no statistically significant association between *XRCC3* T241M polymorphism and prostate cancer risk, but homozygous carriers deserve further study. Relative to men with the TT genotype and a low intake of preserved foods, those with the MT+MM genotype and having a higher intake of nitrosamines and nitrosamine precursors, had a significantly higher risk of prostate cancer (OR=2.6; 95% CI=1.1–6.1). In contrast, men with the MT+MM genotype and a low intake of preserved foods had a significant reduction in risk (OR=0.3; 95% CI=0.1–0.96). These data suggest that diet factors, such as preserved foods, may influence prostate cancer risk in combination with genetic susceptibility in DNA repair pathways.

3.b. Xeroderma pigmentosum complementation group 7 (XRCC7)—XRCC7/PRKDC (protein kinase, DNA-activated, catalytic polypeptide) is a key enzyme that becomes activated upon incubation with DNA. Genetic defects in this enzyme result in immunodeficiency, radiosensitivity, and premature aging [90, 91]. These phenotypes are due to the defect of DNA double strand breaks repair processes. Recent studies reveal that XRCC7 also participates in signal transduction cascades related to apoptotic cell death, telomere maintenance and other pathways of genome surveillance [92]. Only one epidemiological study has been reported, one of the 9 known SNPs [39], only g6721t polymorphism located intron 8 was investigated. No significant association between *XRCC7* g6721t polymorphism and prostate cancer risk was observed in this small hospital-based study of Japanese man [10]. The functional significance of the *XRCC7* g6721t polymorphism is not firmly established, but it may regulate splicing and cause mRNA instability [93].

3.c. Nijmegen breakage syndrome1 (NBS1)—The Nijmegen breakage syndrome 1 (*NBS1*) is part of a protein complex that forms in response to DNA damage to maintain chromosomal integrity. The exact role of NBS1 in DNA repair is not fully understood because NBS1 does not have a DNA binding site or kinase activity, which is usually required in DNA repair. However, the N-terminal domain binds to γH2AX, and this may be an important step to recruit the NBS1 protein complex to the proximity of DNA repair [94]. Thirty-eight polymorphisms in *NBS1* have been reported, including codon E185Q (rs1805794) [39]. Although there is no information regarding changes in the activity of the *NBS1*-185Q variant, the region between amino acid 108–196 of the NBS1 enzyme constitutes a *BRCA1* COOH-terminus domain that is presumably involved in cell-cycle checkpoints or in DNA repair [95]. In this same report, all individuals with the *NBS1* 185QQ genotype had lung tumors with *p53* mutations in contrast with only 46% of *p53* mutations in tumors from individuals with 185EE genotype [95]. In the only study of this variant in relation to prostate cancer, Hebbring *et al.* (2005) observed that *NBS1* E185Q polymorphism was not strongly associated with familial or sporadic prostate cancer risk [29].

4. Direct Reversal (DR) pathway

The biologically significant DNA lesions produced by both carcinogenic and chemotherapeutic alkylating agents are O^6-alkylguanine adducts, which can pair with thymine instead of cytosine during DNA replication. Therefore, O^6-alkylguanine adducts may be responsible for the increase in the frequency of mutations following exposure to alkylating agents, and carcinogenesis [96].

4.a. Methylguanine-DNA methyltransferase (MGMT)—The only known enzyme in the DR pathway is methylguanine-DNA methyltransferase (MGMT). MGMT transfers the alkyl group at the O^6 position of guanine to a cysteine residue within its active site, leading to the direct restoration of the natural chemical composition of DNA without the need for genomic reconstruction. Defective MGMT activity often increases mutation because O^6-MeG mispairs with thymine during DNA replication [88].

Among 16 SNPs in *MGMT* [39], the functional effects of two common SNPs (L84F and I143V) have been examined [12]. Although L84F polymorphism did not affect cell survival after exposure to *N*-methyl-*N*-nitro-*N*-nitrosoguanidine [97], *MGMT* 143V allele was significantly more resistant to inactivation by MGMT pseudosubstrate, O^6-(4-bromothenyl)guanine [98]. However, Liu et al (2003) reported that the relative gene expression level, evaluated by the real-time reverse transcription-PCR assay of MGMT in peripheral lymphocytes, was not significantly different between in prostate cancer patients

and age- and ethnicity-matched controls [21]. Further, this I143V change may affect the isoleucine residue close to the alkyl acceptor cysteine residue at codon 145 [96].

Ritchey *et al.* (2005) examined *MGMT* L84F and I143V polymorphisms in a population-based case-control study of Chinese (162 cases, 251 controls). The *MGMT* L84F polymorphism was significantly associated with a 2 fold increased risk, but the I143V polymorphism was not [12].

5. Damage recognition cell cycle delay responses

Minimizing transmission of DNA mutation to daughter cells is biologically important. Therefore, some enzymes can recognize DNA damage and signal the status to initiate DNA replication [88]. DNA damage activates a cell cycle delay response pathway to earn time for damage repair [99]. Defects in this pathway may result in genomic instability, ultimately leading to cancer susceptibility. The key enzyme of this damage recognition cell delay response pathway is the ataxia telangiectasia-mutated (ATM) and the tumor suppressor protein p53.

5.a. Ataxia telangiectasia mutated protein (ATM)—ATM, which is the product of the gene mutated in patients with the autosomal recessive disorder ataxia telangiectasia, is one of key enzymes responsible for downstream signaling. ATM is activated by DNA damage and induces the trans-activation of various proteins involved in cell cycle arrest, apoptosis, DNA repair and centrosome duplication. In particular, ATM regulates phosphorylation of p53 protein, thereby allowing p53 to accumulate. ATM also regulates a wide variety of downstream proteins, including the tumor suppressor BRCA1, checkpoint kinase CHK2, checkpoint protein RAD50 and DNA repair protein *NBS1* [100]. Nine polymorphisms in ATM have been reported [39]. Angele *et al.* (2004) investigated the association of 5 SNPs in ATM (D1853N, D1853V, ivs38-8t>c, ivs38-15g>c and P1054R) with prostate cancer risk [30]. The ATM P1054R variant is located in the beta-adaptin domain of the ATM protein and has been suggested to be linked to an increased cancer risk, particularly breast cancer [101, 102]. Only ATM 1054R allele was significantly associated with an increased risk of prostate cancer [30]. Further, in the same study, a lymphoblastoid cell line carrying P1054R polymorphism shows a significantly different cell progression to that seen in cell lines carry a wild type ATM after exposure to ionizing radiation. These results suggest that codon 1054 polymorphism confers an altered cellular phenotype and might be associated with prostate cancer risk.

6. Oligogenic Model

Results of epidemiological studies have been inconsistent. Although the exact basis for the inconsistency is unknown, a number of factors may be relevant, including various study design limitations (e.g., using mixed ethnic groups, polymorphisms with unknown functional effects, enzymes not expressed in target tissues, and use of prevalent cases), competing or overlapping DNA repair pathways, and grouping of genotypes, small sample sizes, or variations in allelic frequencies across populations. Many of the studies used convenience samples of cases and controls. However, one of main potential reasons is investigating only one SNP and one gene from a complex metabolic pathway.

Due to recent advance in high-throughput genotyping techniques, multiple polymorphisms within genes, multiple genes in the same pathway, and haplotype approaches are now available to greatly increase the depth of exploration. Although several studies analyze multiple SNPs within a gene, only two studies used a haplotype analysis [10, 11]. A few studies also analyzed multiple genes in the DNA repair pathway. This approach may provide

more biologically plausible insight into the studied associations, including interaction effects of different alleles on prostate cancer risk.

When prostate cancer risk for combined effects of multiple polymorphisms in different DNA repair genes were estimated, we often find significant associations. Rybicki et al. (2004) reported that the OR for the combined effects of the *XPD* 312 DD and *XRCC1* 399 QQ genotype was 4.8 compared with *XPD* 312 DN/NN and *XRCC1* RR/RQ genotypes [13]. In a separate study, similar combined effects were observed in individuals with *APE1* D148E/*XRCC1* R399Q polymorphisms. The OR for the combined effects of the *APE1* 51QQ and *XRCC1* 399RQ/QQ genotypes was 4.0 compared with *APE1* QH/HH and *XRCC1* 399RR [11]. Recently, Hirata et al. (2007) reported that significant combined effects of SNPs in *XPC* and *XRCC1* when two genes from different DNA repair pathway, were observed [10].

These combined effect with multiple SNPs and different genes suggest that severely defected DNA repair capacity may play a role in prostate cancer risk, particularly when the function of multiple DNA repair genes are compromised.

DISCUSSION

Fifteen published epidemiological studies have presented the association of 31 SNPs in 14 DNA repair genes with prostate cancer risk. Although more studies are warranted, the only pathway that shows significant associations is BER. The XRCC*1* 399Q allele is associated with increased risk for carriers alone or when the variant allele is combined with other DNA repair polymorphisms or low antioxidant diet [10–13, 15, 27]. Lockett *et al.* (2004) reported that *ADPRT* V762A variant contributed to prostate cancer risk and altered enzyme activity [28]. The *hOGG1* S326C polymorphism needs additional studies. Particularly, results from epidemiological studies of other cancer sites show a consistent relation with increased risk [51–63].

SNPs in two NER genes, *XPC* and *XPD*, show significant associations with prostate cancer risk in some [10, 13], but not all studies [17]. Finally, a study from ataxia telangiectasia mutated protein (ATM) show a promising result [30].

Epidemiological studies of SNPs in DNA repair genes may inform individual susceptibility and provide insight on potential mechanisms of carcinogenesis. The current challenge is to validate the functional impact of important SNPs identified by epidemiological studies. Another challenge is to identify “causal SNPs” through epidemiological studies, especially in studies investigating the role of SNPs in complex prostate cancer. Results of many epidemiological studies are non-significant or border-line significant risk estimates. Most studies do not have enough power to investigate gene-gene and gene-environmental interactions. Studies investigating a single SNP in a DNA repair gene are not likely detecting difference of overall DNA repair activity. As we presented in the oligogenic model section, a large studies investigating multi-SNPs and multi-genes will generate significant data through combined genotype and haplotype analysis.

In the future, with a combination of relatively inexpensive high-throughput genotyping methods and more functional data will be available based on an individual’s genetic profile that affects the progression, metastasis, and response to therapy. The interpretation of epidemiological data and translation to patient care will be accelerated through pooled analysis and consortia.

References

1. American, CS. Cancer Facts & Figures 2007. A.C. Society. , editor. Atlanta, GA: 2007.
2. Hsing AW, Tsao L, Devesa SS. International trends and patterns of prostate cancer incidence and mortality. Int J Cancer. 2000; 85(1):60–67. [PubMed: 10585584]
3. Crawford ED. Epidemiology of prostate cancer. Urology. 2003; 62 Suppl 1(6):3–12. [PubMed: 14706503]
4. Noble RL. The development of prostatic adenocarcinoma in Nb rats following prolonged sex hormone administration. Cancer Res. 1977; 37(6):1929–1933. [PubMed: 858144]
5. Henderson BE, Ross RK, Pike MC, Casagrande JT. Endogenous hormones as a major factor in human cancer. Cancer Res. 1982; 42(8):3232–3239. [PubMed: 7046921]
6. Friedberg EC. How nucleotide excision repair protects against cancer. Nat Rev Cancer. 2001; 1(1): 22–33. [PubMed: 11900249]
7. Mullaart E, Lohman PH, Berends F, Vijg J. DNA damage metabolism and aging. Mutat Res. 1990; 237(5–6):189–210. [PubMed: 2079959]
8. Wood RD, Mitchell M, Sgouros J, Lindahl T. Human DNA repair genes. Science. 2001; 291(5507): 1284–1289. [PubMed: 11181991]
9. Goode EL, Ulrich CM, Potter JD. Polymorphisms in DNA repair genes and associations with cancer risk. Cancer Epidemiol Biomarkers Prev. 2002; 11(12):1513–1530. [PubMed: 12496039]
10. Hirata H, et al. Polymorphisms of DNA repair genes are risk factors for prostate cancer. Eur J Cancer. 2007; 43(2):231–237. [PubMed: 17196815]
11. Chen L, Ambrosone CB, Lee J, Sellers TA, Pow-Sang J, Park JY. Association between polymorphisms in the DNA repair genes XRCC1 and APE1, and the risk of prostate cancer in white and black Americans. J Urol. 2006; 175(1):108–112. discussion 112. [PubMed: 16406883]
12. Ritchey JD, et al. Genetic variants of DNA repair genes and prostate cancer: a population-based study. Cancer Epidemiol Biomarkers Prev. 2005; 14(7):1703–1709. [PubMed: 16030105]
13. Rybicki BA, Conti DV, Moreira A, Cicek M, Casey G, Witte JS. DNA repair gene XRCC1 and XPD polymorphisms and risk of prostate cancer. Cancer Epidemiol Biomarkers Prev. 2004; 13(1): 23–29. [PubMed: 14744728]
14. Chen L, Elahi A, Pow-Sang J, Lazarus P, Park J. Association between polymorphism of human oxoguanine glycosylase 1 and risk of prostate cancer. J Urol. 2003; 170(6 Pt 1):2471–2474. [PubMed: 14634453]
15. van Gils CH, Bostick RM, Stern MC, Taylor JA. Differences in base excision repair capacity may modulate the effect of dietary antioxidant intake on prostate cancer risk: an example of polymorphisms in the XRCC1 gene. Cancer Epidemiol Biomarkers Prev. 2002; 11(11):1279–1284. [PubMed: 12433703]
16. Xu J, et al. Associations between hOGG1 sequence variants and prostate cancer susceptibility. Cancer Res. 2002; 62(8):2253–2257. [PubMed: 11956079]
17. Lockett KL, Snowhite IV, Hu JJ. Nucleotide-excision repair and prostate cancer risk. Cancer Lett. 2005; 220(2):125–135. [PubMed: 15766587]
18. Nock NL, et al. Polymorphisms in estrogen bioactivation, detoxification and oxidative DNA base excision repair genes and prostate cancer risk. Carcinogenesis. 2006; 27(9):1842–1848. [PubMed: 16569655]
19. Xu Z, et al. Relationship between DNA repair gene XRCC1 Arg399Gln polymorphism and susceptibility to prostate cancer in the Han population in Jiangsu and Anhui. Zhonghua Nan Ke Xue. 2007; 13(4):327–331. [PubMed: 17491266]
20. Bau DT, et al. Association of XPD polymorphisms with prostate cancer in Taiwanese patients. Anticancer Res. 2007; 27(4C):2893–2896. [PubMed: 17695467]
21. Liu Z, et al. Overexpression of hMTH in peripheral lymphocytes and risk of prostate cancer: a case-control analysis. Mol Carcinog. 2003; 36(3):123–129. [PubMed: 12619034]
22. Strom SS, Spitz MR, Yamamura Y, Babaian RJ, Scardino PT, Wei Q. Reduced expression of hMSH2 and hMLH1 and risk of prostate cancer: a case-control study. Prostate. 2001; 47(4):269–275. [PubMed: 11398174]

23. Chen Y, et al. Alterations in PMS2, MSH2 and MLH1 expression in human prostate cancer. Int J Oncol. 2003; 22(5):1033–1043. [PubMed: 12684669]
24. Chen Y, et al. Defects of DNA mismatch repair in human prostate cancer. Cancer Res. 2001; 61(10):4112–4121. [PubMed: 11358834]
25. Hu JJ, et al. Deficient nucleotide excision repair capacity enhances human prostate cancer risk. Cancer Res. 2004; 64(3):1197–1201. [PubMed: 14871857]
26. Nam RK, et al. The use of genetic markers to determine risk for prostate cancer at prostate biopsy. Clin Cancer Res. 2005; 11(23):8391–8397. [PubMed: 16322300]
27. Goodman M, et al. Lycopene intake and prostate cancer risk: effect modification by plasma antioxidants and the XRCC1 genotype. Nutr Cancer. 2006; 55(1):13–20. [PubMed: 16965236]
28. Lockett KL, et al. The ADPRT V762A genetic variant contributes to prostate cancer susceptibility and deficient enzyme function. Cancer Res. 2004; 64(17):6344–6348. [PubMed: 15342424]
29. Hebbring SJ, et al. Role of the nijmegen breakage syndrome 1 gene in familial and sporadic prostate cancer. Cancer Epidemiol Biomarkers Prev. 2006; 15(5):935–938. [PubMed: 16702373]
30. Angele S, et al. ATM polymorphisms as risk factors for prostate cancer development. Br J Cancer. 2004; 91(4):783–787. [PubMed: 15280931]
31. Xu Z, et al. Relationship between XRCC1 polymorphisms and susceptibility to prostate cancer in men from Han, Southern China. Asian J Androl. 2007; 9(3):331–338. [PubMed: 17486273]
32. Demple B, Harrison L. Repair of oxidative damage to DNA: enzymology and biology. Annu Rev Biochem. 1994; 63:915–948. [PubMed: 7979257]
33. Robson CN, Hickson ID. Isolation of cDNA clones encoding a human apurinic/apyrimidinic endonuclease that corrects DNA repair and mutagenesis defects in E. coli xth (exonuclease III) mutants. Nucleic Acids Res. 1991; 19(20):5519–5523. [PubMed: 1719477]
34. Wilson DM 3rd, Barsky D. The major human abasic endonuclease: formation, consequences and repair of abasic lesions in DNA. Mutat Res. 2001; 485(4):283–307. [PubMed: 11585362]
35. Boiteux S, Radicella JP. The human OGG1 gene: structure, functions, and its implication in the process of carcinogenesis. Arch Biochem Biophys. 2000; 377(1):1–8. [PubMed: 10775435]
36. Sunaga N, et al. OGG1 protein suppresses G:C-->T:A mutation in a shuttle vector containing 8-hydroxyguanine in human cells. Carcinogenesis. 2001; 22(9):1355–1362. [PubMed: 11532855]
37. Lindahl T, Wood RD. Quality control by DNA repair. Science. 1999; 286(5446):1897–1905. [PubMed: 10583946]
38. Kohno T, et al. Genetic polymorphisms and alternative splicing of the hOGG1 gene, that is involved in the repair of 8-hydroxyguanine in damaged DNA. Oncogene. 1998; 16(25):3219–3225. [PubMed: 9681819]
39. NCBI. SNP500 Cancer. Cancer Genome Anatomy Project. 2006. p. http://snp500cancer.nci.nih.gov.
40. Shinmura K, Kohno T, Kasai H, Koda K, Sugimura H, Yokota J. Infrequent mutations of the hOGG1 gene, that is involved in the excision of 8-hydroxyguanine in damaged DNA, in human gastric cancer. Jpn J Cancer Res. 1998; 89(8):825–828. [PubMed: 9765618]
41. Janssen K, Schlink K, Gotte W, Hippler B, Kaina B, Oesch F. DNA repair activity of 8-oxoguanine DNA glycosylase 1 (OGG1) in human lymphocytes is not dependent on genetic polymorphism Ser326/Cys326. Mutat Res. 2001; 486(3):207–216. [PubMed: 11459633]
42. Dherin C, Radicella JP, Dizdaroglu M, Boiteux S. Excision of oxidatively damaged DNA bases by the human alpha-hOgg1 protein and the polymorphic alpha-hOgg1(Ser326Cys) protein which is frequently found in human populations. Nucleic Acids Res. 1999; 27(20):4001–4007. [PubMed: 10497264]
43. Hardie LJ, et al. The effect of hOGG1 and glutathione peroxidase I genotypes and 3p chromosomal loss on 8-hydroxydeoxyguanosine levels in lung cancer. Carcinogenesis. 2000; 21(2):167–172. [PubMed: 10657953]
44. Park YJ, Choi EY, Choi JY, Park JG, You HJ, Chung MH. Genetic changes of hOGG1 and the activity of oh8Gua glycosylase in colon cancer. Eur J Cancer. 2001; 37(3):340–346. [PubMed: 11239755]

45. Kondo S, et al. Overexpression of the hOGG1 gene and high 8-hydroxy-2'-deoxyguanosine (8-OHdG) lyase activity in human colorectal carcinoma: regulation mechanism of the 8-OHdG level in DNA. Clin Cancer Res. 2000; 6(4):1394–1400. [PubMed: 10778969]
46. Blons H, et al. Frequent allelic loss at chromosome 3p distinct from genetic alterations of the 8-oxoguanine DNA glycosylase 1 gene in head and neck cancer. Mol Carcinog. 1999; 26(4):254–260. [PubMed: 10569802]
47. Hu YC, Ahrendt SA. hOGG1 Ser326Cys polymorphism and G:C-to-T:A mutations: no evidence for a role in tobacco-related non small cell lung cancer. Int J Cancer. 2005; 114(3):387–393. [PubMed: 15551330]
48. Tarng DC, Tsai TJ, Chen WT, Liu TY, Wei YH. Effect of human OGG1 1245C-->G gene polymorphism on 8-hydroxy-2'-deoxyguanosine levels of leukocyte DNA among patients undergoing chronic hemodialysis. J Am Soc Nephrol. 2001; 12(11):2338–2347. [PubMed: 11675410]
49. Chen SK, et al. Age-associated decrease of oxidative repair enzymes, human 8-oxoguanine DNA glycosylases (hOgg1), in human aging. J Radiat Res (Tokyo). 2003; 44(1):31–35. [PubMed: 12841596]
50. Yamane A, et al. Differential ability of polymorphic OGG1 proteins to suppress mutagenesis induced by 8-hydroxyguanine in human cell in vivo. Carcinogenesis. 2004; 25(9):1689–1694. [PubMed: 15073047]
51. Xing DY, Tan W, Song N, Lin DX. Ser326Cys polymorphism in hOGG1 gene and risk of esophageal cancer in a Chinese population. Int J Cancer. 2001; 95(3):140–143. [PubMed: 11307145]
52. Sugimura H, et al. hOGG1 Ser326Cys polymorphism and lung cancer susceptibility. Cancer Epidemiol Biomarkers Prev. 1999; 8(8):669–674. [PubMed: 10744126]
53. Wikman H, et al. hOGG1 polymorphism and loss of heterozygosity (LOH): significance for lung cancer susceptibility in a caucasian population. Int J Cancer. 2000; 88(6):932–927. [PubMed: 11093817]
54. Ito H, et al. A limited association of OGG1 Ser326Cys polymorphism for adenocarcinoma of the lung. J Epidemiol. 2002; 12(3):258–265. [PubMed: 12164330]
55. Le Marchand L, Donlon T, Lum-Jones A, Seifried A, Wilkens LR. Association of the hOGG1 Ser326Cys polymorphism with lung cancer risk. Cancer Epidemiol Biomarkers Prev. 2002; 11(4): 409–412. [PubMed: 11927502]
56. Sunaga N, et al. Contribution of the NQO1 and GSTT1 polymorphisms to lung adenocarcinoma susceptibility. Cancer Epidemiol Biomarkers Prev. 2002; 11(8):730–738. [PubMed: 12163326]
57. Lan Q, et al. Oxidative damage-related genes AKR1C3 and OGG1 modulate risks for lung cancer due to exposure to PAH-rich coal combustion emissions. Carcinogenesis. 2004; 25(11):2177–2181. [PubMed: 15284179]
58. Park J, Chen L, Tockman MS, Elahi A, Lazarus P. The human 8-oxoguanine DNA N-glycosylase 1 (hOGG1) DNA repair enzyme and its association with lung cancer risk. Pharmacogenetics. 2004; 14(2):103–109. [PubMed: 15077011]
59. Hung RJ, et al. Large-scale investigation of base excision repair genetic polymorphisms and lung cancer risk in a multicenter study. J Natl Cancer Inst. 2005; 97(8):567–576. [PubMed: 15840879]
60. Cho EY, et al. Nasopharyngeal carcinoma and genetic polymorphisms of DNA repair enzymes XRCC1 and hOGG1. Cancer Epidemiol Biomarkers Prev. 2003; 12(10):1100–1104. [PubMed: 14578150]
61. Hao B, et al. Identification of genetic variants in base excision repair pathway and their associations with risk of esophageal squamous cell carcinoma. Cancer Res. 2004; 64(12):4378–4384. [PubMed: 15205355]
62. Elahi A, Zheng Z, Park J, Eyring K, McCaffrey T, Lazarus P. The human OGG1 DNA repair enzyme and its association with orolaryngeal cancer risk. Carcinogenesis. 2002; 23(7):1229–1234. [PubMed: 12117782]
63. Kim JI, et al. hOGG1 Ser326Cys polymorphism modifies the significance of the environmental risk factor for colon cancer. World J Gastroenterol. 2003; 9(5):956–960. [PubMed: 12717837]

64. Wang Y, Spitz MR, Zhu Y, Dong Q, Shete S, Wu X. From genotype to phenotype: correlating XRCC1 polymorphisms with mutagen sensitivity. DNA Repair (Amst). 2003; 2(8):901–908. [PubMed: 12893086]

65. Matullo G, et al. DNA repair gene polymorphisms, bulky DNA adducts in white blood cells and bladder cancer in a case-control study. Int J Cancer. 2001; 92(4):562–567. [PubMed: 11304692]

66. Hu JJ, Smith TR, Miller MS, Mohrenweiser HW, Golden A, Case LD. Amino acid substitution variants of APE1 and XRCC1 genes associated with ionizing radiation sensitivity. Carcinogenesis. 2001; 22(6):917–922. [PubMed: 11375899]

67. Hu JJ, Smith TR, Miller MS, Lohman K, Case LD. Genetic regulation of ionizing radiation sensitivity and breast cancer risk. Environ Mol Mutagen. 2002; 39(2–3):208–215. [PubMed: 11921191]

68. Lunn RM, Bell DA, Mohler JL, Taylor JA. Prostate cancer risk and polymorphism in 17 hydroxylase (CYP17) and steroid reductase (SRD5A2). Carcinogenesis. 1999; 20(9):1727–1731. [PubMed: 10469617]

69. Lunn RM, Langlois RG, Hsieh LL, Thompson CL, Bell DA. XRCC1 polymorphisms: effects on aflatoxin B1-DNA adducts and glycophorin A variant frequency. Cancer Res. 1999; 59(11):2557–2561. [PubMed: 10363972]

70. Matullo G, et al. XRCC1, XRCC3, XPD gene polymorphisms, smoking and (32)P-DNA adducts in a sample of healthy subjects. Carcinogenesis. 2001; 22(9):1437–1445. [PubMed: 11532866]

71. Fan J, Otterlei M, Wong HK, Tomkinson AE, Wilson DM 3rd. XRCC1 co-localizes and physically interacts with PCNA. Nucleic Acids Res. 2004; 32(7):2193–2201. [PubMed: 15107487]

72. Tuimala J, Szekely G, Gundy S, Hirvonen A, Norppa H. Genetic polymorphisms of DNA repair and xenobiotic-metabolizing enzymes: role in mutagen sensitivity. Carcinogenesis. 2002; 23(6): 1003–1008. [PubMed: 12082022]

73. Xi T, Jones IM, Mohrenweiser HW. Many amino acid substitution variants identified in DNA repair genes during human population screenings are predicted to impact protein function. Genomics. 2004; 83(6):970–979. [PubMed: 15177551]

74. Hadi MZ, Coleman MA, Fidelis K, Mohrenweiser HW, Wilson DM 3rd. Functional characterization of Ape1 variants identified in the human population. Nucleic Acids Res. 2000; 28(20):3871–3879. [PubMed: 11024165]

75. Dantzer F, et al. Involvement of poly(ADP-ribose) polymerase in base excision repair. Biochimie. 1999; 81(1–2):69–75. [PubMed: 10214912]

76. Wieler S, Gagne JP, Vaziri H, Poirier GG, Benchimol S. Poly(ADP-ribose) polymerase-1 is a positive regulator of the p53-mediated G1 arrest response following ionizing radiation. J Biol Chem. 2003; 278(21):18914–18921. [PubMed: 12642583]

77. Caldecott KW, McKeown CK, Tucker JD, Ljungquist S, Thompson LH. An interaction between the mammalian DNA repair protein XRCC1 and DNA ligase III. Mol Cell Biol. 1994; 14(1):68–76. [PubMed: 8264637]

78. Sancar GB, Siede W, van Zeeland AA. Repair and processing of DNA damage: a summary of recent progress. Mutat Res. 1996; 362(1):127–146. [PubMed: 8538644]

79. Yu MW, et al. Polymorphisms in XRCC1 and glutathione S-transferase genes and hepatitis B-related hepatocellular carcinoma. J Natl Cancer Inst. 2003; 95(19):1485–1488. [PubMed: 14519756]

80. Spitz MR, et al. Modulation of nucleotide excision repair capacity by XPD polymorphisms in lung cancer patients. Cancer Res. 2001; 61(4):1354–1357. [PubMed: 11245433]

81. Baccarelli A, et al. XPD gene polymorphism and host characteristics in the association with cutaneous malignant melanoma risk. Br J Cancer. 2004; 90(2):497–502. [PubMed: 14735199]

82. Benhamou S, Sarasin A. ERCC2 /XPD gene polymorphisms and lung cancer: a HuGE review. Am J Epidemiol. 2005; 161(1):1–14. [PubMed: 15615908]

83. Hou SM, et al. The XPD variant alleles are associated with increased aromatic DNA adduct level and lung cancer risk. Carcinogenesis. 2002; 23(4):599–603. [PubMed: 11960912]

84. Lunn RM, et al. XPD polymorphisms: effects on DNA repair proficiency. Carcinogenesis. 2000; 21(4):551–555. [PubMed: 10753184]

85. Duell EJ, et al. Polymorphisms in the DNA repair genes XRCC1 and ERCC2 and biomarkers of DNA damage in human blood mononuclear cells. Carcinogenesis. 2000; 21(5):965–971. [PubMed: 10783319]
86. Kiyohara C, Yoshimasu K. Genetic polymorphisms in the nucleotide excision repair pathway and lung cancer risk: A meta-analysis. Int J Med Sci. 2007; 4(2):59–71. [PubMed: 17299578]
87. Huang WY, et al. Nucleotide excision repair gene polymorphisms and risk of advanced colorectal adenoma: XPC polymorphisms modify smoking-related risk. Cancer Epidemiol Biomarkers Prev. 2006; 15(2):306–311. [PubMed: 16492920]
88. Mohrenweiser HW, Wilson DM 3rd, Jones IM. Challenges and complexities in estimating both the functional impact and the disease risk associated with the extensive genetic variation in human DNA repair genes. Mutat Res. 2003; 526(1–2):93–125. [PubMed: 12714187]
89. Araujo FD, Pierce AJ, Stark JM, Jasin M. Variant XRCC3 implicated in cancer is functional in homology-directed repair of double-strand breaks. Oncogene. 2002; 21(26):4176–4180. [PubMed: 12037675]
90. Nonoyama S, Ochs HD. Immune deficiency in SCID mice. Int Rev Immunol. 1996; 13(4):289–300. [PubMed: 8884426]
91. Nicolas N, et al. A human severe combined immunodeficiency (SCID) condition with increased sensitivity to ionizing radiations and impaired V(D)J rearrangements defines a new DNA recombination/repair deficiency. J Exp Med. 1998; 188(4):627–634. [PubMed: 9705945]
92. Dip R, Naegeli H. More than just strand breaks: the recognition of structural DNA discontinuities by DNA-dependent protein kinase catalytic subunit. Faseb J. 2005; 19(7):704–715. [PubMed: 15857885]
93. Sipley JD, Menninger JC, Hartley KO, Ward DC, Jackson SP, Anderson CW. Gene for the catalytic subunit of the human DNA-activated protein kinase maps to the site of the XRCC7 gene on chromosome 8. Proc Natl Acad Sci U S A. 1995; 92(16):7515–7519. [PubMed: 7638222]
94. Zhang Y, Zhou J, Lim CU. The role of NBS1 in DNA double strand break repair, telomere stability, and cell cycle checkpoint control. Cell Res. 2006; 16(1):45–54. [PubMed: 16467875]
95. Medina PP, Ahrendt SA, Pollan M, Fernandez P, Sidransky D, Sanchez-Cespedes M. Screening of homologous recombination gene polymorphisms in lung cancer patients reveals an association of the NBS1-185Gln variant and p53 gene mutations. Cancer Epidemiol Biomarkers Prev. 2003; 12(8):699–704. [PubMed: 12917199]
96. Margison GP, Povey AC, Kaina B, Santibanez Koref MF. Variability and regulation of O6-alkylguanine-DNA alkyltransferase. Carcinogenesis. 2003; 24(4):625–635. [PubMed: 12727789]
97. Inoue R, Abe M, Nakabeppu Y, Sekiguchi M, Mori T, Suzuki T. Characterization of human polymorphic DNA repair methyltransferase. Pharmacogenetics. 2000; 10(1):59–66. [PubMed: 10739173]
98. Margison GP, et al. Quantitative trait locus analysis reveals two intragenic sites that influence O6-alkylguanine-DNA alkyltransferase activity in peripheral blood mononuclear cells. Carcinogenesis. 2005; 26(8):1473–1480. [PubMed: 15831531]
99. Matsuoka S, Rotman G, Ogawa A, Shiloh Y, Tamai K, Elledge SJ. Ataxia telangiectasia-mutated phosphorylates Chk2 in vivo and in vitro. Proc Natl Acad Sci U S A. 2000; 97(19):10389–10394. [PubMed: 10973490]
100. Kim JH, et al. Genetic polymorphisms of ataxia telangiectasia mutated affect lung cancer risk. Hum Mol Genet. 2006; 15(7):1181–1186. [PubMed: 16497724]
101. Koren M, et al. ATM haplotypes and breast cancer risk in Jewish high-risk women. Br J Cancer. 2006; 94(10):1537–1543. [PubMed: 16622469]
102. Lee KM, et al. Genetic polymorphisms of ataxia telangiectasia mutated and breast cancer risk. Cancer Epidemiol Biomarkers Prev. 2005; 14(4):821–825. [PubMed: 15824150]
103. Audebert M, Radicella JP, Dizdaroglu M. Effect of single mutations in the OGG1 gene found in human tumors on the substrate specificity of the Ogg1 protein. Nucleic Acids Res. 2000; 28(14): 2672–2678. [PubMed: 10908322]
104. Chen C, et al. Endogenous sex hormones and prostate cancer risk: a case-control study nested within the Carotene and Retinol Efficacy Trial. Cancer Epidemiol Biomarkers Prev. 2003; 12(12):1410–1416. [PubMed: 14693730]

105. Peng T, et al. Oxidative DNA damage in peripheral leukocytes and its association with expression and polymorphisms of hOGG1: a study of adolescents in a high risk region for hepatocellular carcinoma in China. World J Gastroenterol. 2003; 9(10):2186–2193. [PubMed: 14562375]

106. Khan SG, et al. A new xeroderma pigmentosum group C poly(AT) insertion/deletion polymorphism. Carcinogenesis. 2000; 21(10):1821–1825. [PubMed: 11023539]

107. Wang CY, Jones RF, Debiec-Rychter M, Soos G, Haas GP. Correlation of the genotypes for N-acetyltransferases 1 and 2 with double bladder and prostate cancers in a case-comparison study. Anticancer Res. 2002; 22(6B):3529–3535. [PubMed: 12552951]

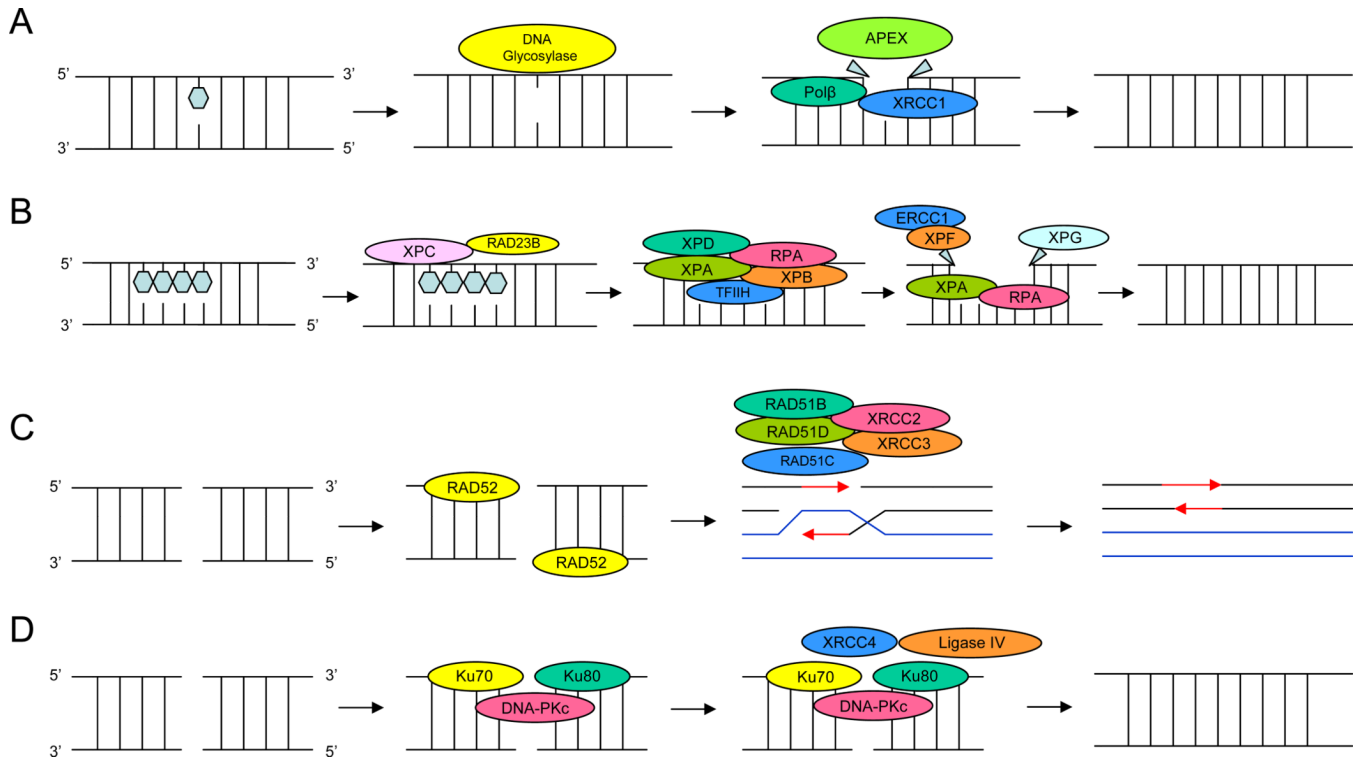

Figure 1.

1A: Base excision repair (BER) pathway targets DNA damaged during replication or by environmental agents. The single damaged base in DNA caused by endogenous metabolism or environmental oxidizing agents result in DNA adducts. Base excision repair involves removing the mutated base out of the DNA and repairing the base alone. **1B:** Nucleotide excision repair (NER) is associated with the repair of bulky adducts induced by several suspected environmental prostate cancer carcinogens. The NER pathway is a complex biochemical process that requires at least four steps: (*a*) damage recognition by a complex of bound proteins including xeroderma pigmentosum complementation group C (XPC), XPA, and replication protein A (RPA); (*b*) unwinding of the DNA by the transcription factor IIH (TFIIH) complex that includes XPD(ERCC2); (*c*) removal of the damaged single-stranded fragment (usually about 27–30 bp) by molecules including an ERCC1 and XPF complex and XPG; and (*d*) synthesis by DNA polymerases. **1C:** Double-strand breaks are produced by replication failure or by DNA damaging agents. Two repair pathways exist to repair double strand breaks. The homologous recombination repair relies on DNA sequence complementarity between the intact chromatid and the damaged chromatid as the bases of stand exchange and repair. **1D:** The non-homologous end-joining repair pathway requires direct DNA joining of the two double-strand-break ends.

Table 1

Epidemiological studies of DNA repair gene SNPs and prostate cancer risk.

Gene	Race	Study design	Case	Control	Genotype Distribution[1]	Comparisons	Adjustment[2]	Odds ration (95%CI)	Ref.
ADPRT V762A	Caucasian	Hospital	438	427	70,26,4 73,25,2	VA vs. VV AA vs. VV	Age, BPH, FH	1.2 (0.9–1.6) 2.7 (1.1–6..5)	[28]
	African Americans	Hospital	50	97	90,10,0 91,9,0	VA vs. VV AA vs. VV		1.0 (0.2–4.0) NA	
APE1 D148E	Caucasian	Hospital	228	219	28,54,18 34,50,16	DE vs. DD EE vs. DD	Age, S, FH	1.2 (0.8–1.9) 1.2 (0.7–2.2)	[11]
	African Americans	Population	124	116	34,52,14 38,53,10	DE vs. DD EE vs. DD	Age, S	1.2 (0.7–2.2) 1.6 (0.6–3.8)	
APE1 Q51H	Caucasian	Hospital	228	219	89,10, 1 85,14, 1	QH vs. QQ HH vs. QQ	Age, S, FH	0.6 (0.3–1.2) 0.6 (0.03–14)	[11]
	African Americans	Population	124	116	79,19, 2 71,26, 3	QH vs. QQ HH vs. QQ	Age, S	0.8 (0.4–1.5) 0.7 (0.1–3.1)	
ATM D1853N	Caucasians	Population	637	455	73,24,3 69,28,3	ga vs. gg aa vs. gg	None	0.8 (0.7–1.1) 1.0 (0.5–2.1)	[30]
ATM D1853V	Caucasians	Population	637	455	99,1,0 99,1,0	ta vs. aa	None	0.9 (0.2–3.3)	[30]
ATM ivs38-8t>c	Caucasians	Population	637	455	93,7,0 93,7,0	ct/cc vs. tt	None	1.0 (0.6–1.6)	[30]
ATM ivs38-15g>c	Caucasians	Population	637	455	98,2,0 99,1,0	gc vs. gg	None	1.8 (0.6–5.7)	[30]
ATMP1054R	Caucasians	Population	637	455	92,7,0 96,4,0	PR/RR vs. PP	None	2.1 (1.2–3.9)	[30]
hOGG1 a10660t	Mixed (93% Caucasians)	Hospital	245	222	65,32, 4 61,32, 7	tt vs. aa	Age	NS	[16].
hOGG1 a11657g	Mixed (93% Caucasians)	Hospital	245	222	70,25, 5 74,25, 1	gg vs. aa	Age	9.8 (1.2–76.9)	[16].
	Mixed (84% Caucasians)	Family	159	222	67,29, 5 74,25, 1	gg vs. aa	Age	13.9 (1.6–125)	
hOGG1 a11657g	Mixed (84% Caucasians)	Hospital	996	1092	70,27, 3 71,25, 4	ag vs. aa gg vs. aa	Age	NS	[26]
hOGG1 a11826t	Mixed (93% Caucasians)	Hospital	245	222	66,31, 3 60,33, 7	tt vs. aa	Age	NS	[16].
hOGG1 a7143g	Mixed (93% Caucasians)	Hospital	245	222	68,26, 5 71,28, 1	gg vs. aa	Age	5.1 (1.1–23.3)	[16].

Gene	Race	Study design	Case	Control	Genotype Distribution[1]	Comparisons	Adjustment[2]	Odds ration (95%CI)	Ref.
	Mixed (84% Caucasians)	Family	159	222	64,32, 5 71,28, 1	gg vs. aa	Age	8.2 (1.5–45.5)	
hOGG1 a9110g	Mixed (93% Caucasians)	Hospital	245	222	66,31, 3 60,34, 7	gg vs. aa	Age	NS	[16].
hOGG1 c10629g	Mixed (93% Caucasians)	Hospital	245	222	28,44,27 30,41,30	gg vs. cc	Age	NS	[16].
hOGG1 g3402a	Mixed (93% Caucasians)	Hospital	245	222	40,44,16 43,45,12	aa vs. gg	Age	NS	[16].
hOGG1 g3574a	Mixed (93% Caucasians)	Hospital	245	222	67,28, 5 60,34, 6	aa vs. gg	Age	NS	[16].
hOGG1 g6170c	Mixed (93% Caucasians)	Hospital	245	222	63,33, 4 58,34, 7	cc vs. gg	Age	NS	[16].
hOGG1 S326C	Caucasians	Hospital	84	252	58,35, 7 74,25, 1	SC vs. SS CC vs. SS	Age, S	1.8 (1.0–3.3) 7.8 (1.7–36)	[14]
hOGG1 S326C	Mixed (93% Caucasians)	Hospital	245	222	61,36, 3 55,36, 9	CC vs. SS	Age	0.3 (0.1–0.8)	[16].
	Mixed (84% Caucasians)	Family	159	222	61,35, 4 55,36, 9	CC vs. SS	Age	0.5 (0.2–1.7)	
hOGG1 S326C	Mixed (84% Caucasians)	Hospital	996	1092	60,35, 5 57,35, 8	SC vs. SS CC vs. SS	Age, race, FH, DRE, PSA	0.9 (0.8–1.1) 0.7 (0.5–1.0)	[26]
hOGG1 S326C	Mixed (90% Caucasians)	Family	439	479	64,31, 5 54,30, 6	SC vs. SS CC vs. SS	Age	1.1 (0.7–1.6) 0.7 (0.3–1.7)	[18]
MGMT I143V	Chinese	Population	162	251	96, 3, 1 98, 2, 0	VV/IV vs. II	Age	1.9 (0.6–6.2)	[12]
MGMT L84F	Chinese	Population	162	251	76,22,1 86,13,1	LF vs. LL FF va. LL	Age	2.0 (1.2–3.3) 3.4 (0.3–38.1)	[12]
hHR23B A249V	Mixed (90% Caucasians)	Hospital	494	470	$_{29}$[3]	AA vs. AV/VV	Age,BPH, FH, S	1.1 (0.8–1.4)	[17]
NBS1E185Q	unknown	Family	121	200	33,52,15 44,40,16	EQ vs. EE QQ vs. EE	none	1.4 (0.7–2.8) 0.8 (0.4–1.6)	[29]
		Population	200	200	41,47,12 44,40,16	EQ vs. EE QQ vs. EE		1.6 (0.9–2.9) 1.2 (0.7–2.3)	
XPC A499V	Mixed (90% Caucasians)	Hospital	494	470	$_{24}$[3]	AA/AV vs. VV	Age,BPH, FH, S	0.9(0.5–1.5)	[17]
XPC K939Q	Mixed (90% Caucasians)	Hospital	494	470	$_{38}$[3]	KK/KQ vs. QQ	Age,BPH, FH, S	1.0 (0.7–1.4)	[17]

Gene	Race	Study design	Case	Control	Genotype Distribution[1]	Comparisons	Adjustment[2]	Odds ration (95%CI)	Ref.
XPC K939Q	Japanese	Hospital	165	165	47,47,6 44.42.14	KK/KQ vs. QQ	Age	2.5 (1.1–5.5)	[10]
XPD c-114g	Taiwanese	Hospital	123	479	28,53,19 31,46,23	DN/NN vs. DD		1.0 (0.7–1.5)	[20]
XPD D312N	Mixed	Siblings	637	480	44,45,12 44,48, 8	NN vs. DN/DD	None	1.6 (1.0–2.5)	[13]
	Caucasian	Siblings	572	437	40,47,13 41,50, 9	NN vs. DN/DD	None	1.6 (1.0–2.5)	
XPD D312N	Mixed (90% Caucasians)	Hospital	494	470	41[3]	NN vs. DN/DD	Age,BPH, FH, S	0.8 (0.5–1.2)	[17]
XPD D312N	Taiwanese	Hospital	123	479	50,32,18 65,22,13	DN/NN vs. DD		1.8 (1.2–2.7)	[20]
XPD K751Q	Mixed (90% Caucasians)	Hospital	494	470	35[3]	KQ/QQ vs. KK	Age,BPH, FH, S	0.9 (0.6–1.4)	[17]
XPD K751Q	Chinese	Population	162	251	88,12,0 86,13,1	KQ/QQ vs. KK	Age	0.8 (0.5–1.5)	[12]
XPD K751Q	Mixed	Siblings	637	480	40,47,13 41,47,12	QQ vs. KQ/KK	None	1.1 (0.7–1.8)	[13]
	Caucasian	Siblings	572	437	39,48,13 41,47,12	QQ vs. KQ/KK	None	1.2 (0.7–2.0)	
XPD K751Q	Taiwanese	Hospital	123	479	91,7,2 92,7,1	DN/NN vs. DD		1.3 (0.6–2.5)	[20]
XPF/ERCC4 R415Q	Mixed (90% Caucasians)	Hospital	494	470	9[3]	RQ vs. RR	Age, BPH, S. FH	1.4 (1.0–2.0)	[17]
XPG/ERCC5 D1104H	Mixed (90% Caucasians)	Hospital	494	470	46[3]	DD/DH vs. HH	Age, BPH, S, FH	0.8 (0.5–1.5)	[17]
XRCC1 R194W	Mixed (90% Caucasians)	Population	76	182	88,12,0 84,15,1	RW/WW vs. RR	Age, race	0.7 (0.3–1.6)	[15]
XRCC1 R194W	Japanese	Hospital	165	165	42,48,13 52,38,10	RW/WW vs. RR	Age	1.5 (0.9–2.2)	[10]
XRCC1 R194W	Chinese	Hospital	207	235	50,41,9 39,50,11	RW/WW vs. RR	Age,S,AL FH	0.6 (1.1–2.5)	[31]
XRCC1 R280H	Mixed (90% Caucasians)	Population	76	182	87,13,0 90,10,0	RH vs. RR	Age, race	1.5 (0.7–3.6)	[15]

Methods Mol Biol. Author manuscript; available in PMC 2014 March 28.

Gene	Race	Study design	Case	Control	Genotype Distribution[1]	Comparisons	Adjustment[2]	Odds ration (95%CI)	Ref.
XRCC1 R280H	Chinese	Hospital	207	235	80,19,1 82,17,1	RR/RH vs. HH	Age,S,AL FH	1.1 (0.7–1.9)	[31]
XRCC1 R399Q	Caucasian	Hospital	228	219	42,46,12 50,40,10	RQ vs. RR QQ vs. RR	Age, S, FH	1.6 (1.1–2.5) 1.6 (0.8–3.1)	[11]
	African Americans	Population	124	116	73,24,3 73,24,3	RQ vs. RR QQ vs. RR	Age, S	1.2 (0.6–2.2) 1.5 (0.3–8.2)	
XRCC1 R399Q	Chinese	Hospital	207	235	52,41,7 65,31,4	RR/RQ vs. QQ	Age,S,AL FH	1.7 (1.1–2.5)	[31]
XRCC1 R399Q	Chinese	Population	162	251	55,34,11 54,41,5	RQ vs. RR QQ vs. RR	Age	0.8 (0.5–1.3) 2.2 (1.0–4.8)	[12]
XRCC1 R399Q	Japanese	Hospital	165	165	53,38,9 52,42,6	RQ/QQ vs. RR	Age	1.0 (0.6–1.5)	[10]
XRCC1 R399Q	Mixed	Siblings	637	480	46,43,11 45,43,12	QQ vs. RQ/RR	None	0.9(0.6–1.4)	[13]
	Caucasians	Siblings	572	437	43,45,12 41,46,13	QQ vs. RQ/RR	None	0.9(0.5–1.4)	
XRCC1 R399Q	Mixed (90% Caucasians)	Population	76	182	49,39,12 42,43,15	RQ vs. RR QQ vs. RR	Age, race	0.8 (0.5–1.4) 0.7 (0.3–1.6)	[15]
XRCC1 R399Q	Mixed (92% Caucasians)	Population	77	174	49, (51)[4] 43, (57)	RQ vs. RR QQ vs. RR	none	0.8 (0.4–1.5) 0.7 (0.3–1.7)	[27]
XRCC3 T241M	Chinese	Population	162	251	87,11,2 87,13,1	TM vs. TT MM vs. TT	Age	0.8 (0.5–1.6) 2.2 (0.4–13.7)	[12]
XRCC7 g6721t	Japanese	Hospital	165	165	7,48,45 7,41,52	gt/tt vs. gg	Age	1.0 (0.5–1.2)	[10]

[1] numbers are percentages of each genotypes, and single number indicates percentage of minor allele frequency

[2] BPH benign prostate hyperplasia, FH: family history of prostate cancer, S, Smoking, AL, alcohol

[3] minor allelic frequency

[4] heteozygous and homozygous polymorphic genotypes were combined

Table 2

SNPs in DNA repair genes and their functional relation.

Pathway	Gene	SNP ID#	Minor Allele Frequency			Function	Reference
			White	Black	Asian		
BER	ADPRT V762A	rs1136410	0.11	0.06	0.33	Decrease enzyme activities in response to H_2O_2	[28]
BER	APE1 D148E	rs3136820	0.49	0.32	0.28	Hypersensitivity to ionizing radiation	[66]
BER	APE1 Q51H	rs1048945	0.03	0	0	Regulate the DNA binding activity	[73]
DRCC	ATM P1054R	rs1800057	0.02	0	0	Affect the cellular response after exposure to ionizing radiation	[30]
BER	hOGG1 S326C	rs1052133.	0.23	0.38	0.10	No difference in DNA repair capacity between genotypes. 326Cys allele was associated with a decrease in p53 mutations. Suppression of mutagenesis is lower in hOGG1 326Cys. No difference in adducts between genotypes. Adduct level was higher in CC genotypes	[41–46, 103] [47] [38] [40], [48, 104] [105]
DR	MGMT I143V	rs2308321	0.13	0	0	More resistant to inactivation by MGMT pseudosubstrate, O6-(4-bromothenyl) guanine.	[98]
DR	MGMT L84F	rs12917	0.11	0.17	0.11	No affect on cell survival after exposure to *N*-methyl-*N* '-nitro-*N*-nitrosoguanidine.	[97]
NER	hHR23B A249V	rs1805329	0.15	0.26	0	No affect NER activity by plasmid-based NER assay	[17]
NER	XPC A499V	rs2228000	0.10	0.05	0	Affect NER activity by plasmid-based NER assay	[17]
NER	XPC K939Q	rs2228001	0.13	0.13	0	Linkage disequilibrium with intron 9, 5bp deletion which cause alternative splicing.	[106]
NER	XPD/ERCC2 –c114g	rs3810366	0.42	0.91	0.51	SNP in the promoter region	[20]
NER	XPD/ERCC2 D312N	rs1799793	0.31	0	0.06	Affect NER activity by plasmid-based NER assay	[17]
NER	XPD/ERCC2 K751Q	rs1052559	0.27	0.04	0.17	Higher number of chromatid aberrations. No association in SCE frequency or DNA adduct level. Higher adduct level among never smokers.	[84] [85] [65]
NER	XPF/ERCC4 R415Q	rs1800067	0.05	0	0	Reduced repair of aromatic DNA adducts	[83]
NER	XPG/ERCC5 D1104H	rs17655	0.27	0.44	0.46	Affect NER activity by plasmid-based NER assay	[17]

Pathway	Gene	SNP ID#	Minor Allele Frequency			Function	Reference
			White	Black	Asian		
BER	XRCC1 R194W	rs1799782	0.05	0.24	0.08	No association with DNA-adduct levels, mutation rates, or sensitivity to ionizing radiation Lower bleomycin and benzo(a)pyrene diol epoxide sensitivity *in vitro*.	[66–68, 70] [64]
BER	XRCC1 R280H	rs25489	0.03	0.08	0.06	Higher bleomycin sensitivity	[71, 72]
BER	XRCC1 R399Q	rs25487	0.47	0.45	0.10	Higher levels of aflatoxin B1-DNA adducts and higher bleomycin sensitivity	[68, 70, 107]
DSBR	XRCC3 T241M	rs861539	0.42	0.15	0.24	Hypersensitive to DNA damaging agents	[89]