Hypothesis

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[1]

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Abstract

We propose a hypothesis that differences in base excision repair capacity modulate the effect of dietary antioxidant intake on prostate cancer risk. As a preliminary test of this hypothesis, we conducted a pilot case-control study to evaluate prostate cancer risk in men with polymorphisms in the *XRCC1* gene, a key player in base excision repair, across different strata of antioxidant intake. Seventy-seven prostate cancer patients and 183 community controls, for whom we have detailed dietary information, were frequency matched on age and race. We found a somewhat lower prostate cancer risk for men with one or two copies of the variant alleles at the *XRCC1* codons 194 and 399 than for those who were homozygous for the common allele [codon 194: odds ratio (OR) = 0.8; 95% confidence interval (CI), 0.4–1.8 and codon 399: OR = 0.8; 95% CI, 0.5–1.3]. The variant at codon 280 was associated with a slightly increased prostate cancer risk (OR = 1.5; 95% CI, 0.7–3.6). Only the codon 399 polymorphism occurred frequently enough to investigate its joint effect with antioxidant intake. Prostate cancer risk was highest among men who were homozygous for the common allele at codon 399 and had low dietary intake of vitamin E (OR = 2.4; 95% CI, 1.0–5.6) or lycopene (OR = 2.0; 95% CI, 0.8–4.9), whereas low intake of these antioxidants in men without this genotype hardly increased prostate cancer risk. The polymorphism did not modulate risk associated with low intake of vitamin C, A, or β-carotene. The data give some support for our hypothesis but should be regarded as preliminary, because it is limited by small sample size.

We discuss what kind of data and what kind of studies are needed for future evaluation of this hypothesis.

Introduction

There is increasing evidence that ROS[5] may play an important role in prostate carcinogenesis. This is suggested by several epidemiological studies that reported protective effects of dietary and/or supplemental antioxidants, although results are not entirely consistent. Intake of antioxidants via the diet or as supplements may decrease prostate cancer risk through the inactivation of ROS, thereby protecting the DNA from oxidative damage (1).

With respect to vitamin E, several observational studies have shown that high vitamin E intake and or high vitamin E levels in serum were associated with decreased risk of prostate cancer (2–4) or favorable prognosis of prostate cancer (5, 6). However, this could not be confirmed by some other observational studies (7, 8). Striking results were found in the α-Tocopherol β-Carotene lung cancer trial among smokers, where the α-tocopherol group showed a statistically significant decrease in prostate cancer incidence compared with the placebo group (9). However, it should be noted that prostate cancer was not the primary end point and that this may be a chance finding. A large trial, the Selenium and Vitamin E Chemoprevention Trial, is under way to confirm or refute this finding (10).

Several studies have shown that the intake of tomatoes and tomato-based products is associated with reduced risk of prostate cancer (11–13). Also, plasma levels of lycopene, a compound derived primarily from tomatoes, have been found to be inversely related to prostate cancer risk (4, 14). In a study of serum and tissue lycopene and oxidative products it was shown that prostate cancer patients had significantly lower serum and tissue lycopene levels and lower serum protein thiol levels consistent with increased protein oxidation (15). A recent dietary intervention study of prostate cancer patients showed that tomato sauce led to a decrease in leukocyte and prostate DNA oxidative damage (16). A protective effect could not be confirmed in all of the studies (17, 18). Also, it has not yet been proven that lycopene is mechanistically related to prostate cancer risk or that the relationship is explained by other beneficial compounds present in tomatoes. However, it is known that lycopene is an efficient scavenger of singlet oxygen and has a protective effect on lipid peroxidation and DNA damage in cell culture (19).

Vitamin A appears to be able to inhibit carcinogens in animal models (20), but the epidemiological data on humans are contradictory. Higher intake of vitamin A has been associ-

ated with a lower risk of prostate cancer (21, 22) but also with a slightly increased risk (11, 23, 24). Similarly, laboratory studies indicate that β-carotene, one of the precursors of vitamin A, may have a protective effect on prostate cancer risk (25), but the epidemiological evidence is mixed. Higher intake of β-carotene has been associated with increased risk (9, 23), decreased risk (22, 26), or no effect (11, 21, 27).

Very few studies have examined the relationship between dietary vitamin C intake and prostate cancer risk: one reporting a strong protective effect for higher levels of intake (18), but others reporting no association (17, 27).

Studies on the role of GSTs in prostate carcinogenesis also help to confirm the importance of ROS. GSTs are believed to exert a critical role in cellular protection against oxidative stress (28). It has been shown in prostate cancer cells, but not in normal prostate cells, that the gene coding for the pro-oxidant scavenging enzyme GST-π is extensively methylated, leading to loss of expression (29). There is some evidence that polymorphisms in the *GST-θ* gene also have an effect on prostate cancer risk (30–32).

If free oxygen radicals are overproduced or if antioxidant defense is deficient, *e.g.,* by decreased intake of antioxidants, there may be increased oxidative damage to DNA. Such damage includes base modification leading to mispairing during DNA replication or to replication blockage. Alternatively, these products may attack at the sugar-phosphate backbone, leading to base loss or strand breaks (33).

DNA repair systems play an important role in protecting the genome from oxidative damage. Several different DNA repair systems exist, with the BER pathway specifically targeting "nonbulky" base adducts and single strand breaks, such as those induced by ROS (33). One of the key players in the BER system is the *XRCC1* gene, which has been mapped to human chromosome 19q13.2–13.3 (34, 35). XRCC1 functions as the central scaffolding protein for other key players, including DNA polymerase β (36) and DNA ligase III (36), which are responsible for filling the nucleotide gap and sealing the resulting nick (33). XRCC1 also interacts with poly(ADP-ribose) polymerase (37), a nuclear zinc-finger DNA-binding protein that detects single strand breaks (38) and polynucleotide kinase, which is required for processing damaged DNA termini (39).

We propose a hypothesis that low antioxidant intake puts men at higher risk of prostate cancer if they have reduced BER capacity relative to men with normal repair. Interindividual variation in DNA repair capacity could be because of polymorphisms in genes coding for proteins in the BER system. As a preliminary test of this hypothesis we conducted a pilot case-control study in which we evaluated prostate cancer risk in men with polymorphisms in *XRCC1* across different strata of intake of antioxidants. Three common polymorphisms leading to amino acid substitutions have been described for the *XRCC1* gene (40): one at codon 194 (*Arg→Trp*), one at codon 280 (*Arg→His*), and one at codon 399 (*Arg→Gln*). The functional significance of these polymorphisms remains unclear, although they all occur at amino acid residues that are highly conserved across human, hamster, and mouse (41), suggesting that they are in regions important to the protein function. In epidemiological studies, these polymorphisms have been found to be associated with risk of several cancer types (42–47), although the results are not entirely consistent.

Materials and Methods

Study Population. The study population for this case-control study has been described previously (48). Briefly, all of the participants were residents from the Piedmont Triad metropolitan area and were age 50 or older. Participants were excluded if they had a history of previous cancer (other than nonmelanoma skin cancer), had current prostatic disease, or had a previous prostate surgery. The reason for this was that diseases such as benign prostatic hyperplasia or prostatitis potentially influence prostate cancer risk and could be related to the genotype as well.

Cases had a biopsy-proven first diagnosis of incident prostate cancer, and were identified through area urology and radiation oncology practices within days of diagnosis. They were studied before treatment. Controls were randomly selected from community directories for the Piedmont Triad area. A letter and brochure were sent to randomly selected men, followed by a telephone call within 2 weeks (up to 10 calls at various times of day). They were frequency matched with cases on age (5-year intervals), race, and zip code.

Participants were accrued from February 1994 through January 1996. Of 203 case subjects who were initially found to be eligible, 112 (55%) were interviewed. Attrition was because of refusal or nonresponse (34%), inability to come for the study visit (6%), or cases eventually refused or did not pass final eligibility assessed during the study visit (4%). Of the 877 eligible control subjects, 258 were interviewed (29%). Again, attrition was because of refusal or nonresponse (67%), or controls eventually refused or did not pass final eligibility during the study visit (4%). Blood samples were available for 77 of the 112 participating case subjects (69%) and 183 of the 258 participating control subjects (71%).

Data Collection. Information on medical history, lifestyle, and dietary intake was obtained through interview-assisted questionnaires. For dietary intake the Block-National Cancer Institute Health Habits and History Questionnaire was used (49). This is a standardized food frequency questionnaire developed to determine an individual's dietary intake in the previous year (as a proxy for usual dietary intake). Using Health Habits and History Questionnaire-Dietsys analysis software (National Cancer Institute) daily intakes of vitamin C, vitamin E, vitamin A, β-carotene, lycopene, and calories were estimated. We also tried to estimate the intake of total fat, saturated fat, linoleic acid, and oleic acid, because some earlier studies showed that dietary fat consumption may be related to prostate cancer risk as well, but results are inconclusive (50). It has been suggested that a relationship, if existing at all, could be explained through an increase in oxidative damage (51, 52).

DNA was extracted from peripheral blood lymphocytes. *XRCC1* genotypes were determined as described previously (53). Prostate tumors were classified according to TNM stage. We used this classification to investigate whether relationships were different for higher stage (TNM stage II or higher) and lower stage (TNM stage I) tumors.

Statistical Analysis. Descriptive statistics were calculated for demographic and health-related characteristics of cases and controls, as well as for their daily dietary antioxidant intake. In these and all additional analyses, all of the dietary intake variables were adjusted for energy intake by the regression method of Willett and Stampfer (54). Differences in categorical variables were evaluated by χ^2 tests, differences in normally distributed variables by *t* tests, and continuous variables with a skewed distribution by Wilcoxon rank-sum tests. All tests of statistical significance were two-sided.

Table 1   Dietary antioxidant intake[a] of prostate cancer cases and controls

Dietary intake of	Cases (n = 77)	Controls (n = 183)	P[b]
Vitamin C, g/day[c]	116 (93–157)	130 (92–170)	0.29
Vitamin E, mg α-TE/day[c]	10 (9–13)	11 (9–13)	0.28
Vitamin A, IU/day[c]	7,588 (5,517–10,858)	7,483 (5,752–10,655)	0.97
β-Carotene, μg/day[c]	3,075 (1,912–4,892)	3,099 (2,182–4,682)	0.52
Lycopene, μg/day[c]	817 (488–1,353)	1,120 (630–1,802)	0.02

[a] Values adjusted for energy intake according to regression method of Willett and Stampfer (54).
[b] Based on Wilcoxon's rank-sum test.
[c] Median (interquartile range).

Logistic regression models were used to estimate the ORs and 95% CIs for the main effect of the genotypes on prostate cancer risk. These effects were adjusted for age as a continuous variable, and for ethnicity. Two persons who classified themselves as other than black or white were excluded from the analyses.

To examine whether the effects of intake of antioxidants on prostate cancer risk were modified by *XRCC1* genotypes we used multivariate logistic regression models in which the reference group consisted of subjects with the putative low-risk genotype and low dietary antioxidant intake. The division between low and high dietary antioxidant intake was based on the median value of the antioxidant intake in the control group.

To adjust for potential confounders all of the interaction models included: age, ethnicity, history of prostate cancer in a first-degree relative, education, whether the subject had ever been a farmer, and body mass index. In addition, the combined effect of the genotype and dietary antioxidant intake was adjusted for dietary fat intake. Furthermore, for all of the energy-adjusted variables, energy intake was also included in the multivariate model, in accordance with the method described by Willett and Stampfer (54). All of the analyses were done using SAS software (SAS Institute, Cary, NC).

Results

Cases and controls in this study were similar with respect to age (median age 68 and 67 years, respectively; *P* = 0.24) and ethnicity (91% and 92% whites, respectively; *P* = 0.68), on which they were frequency-matched. They were also similar with respect to body mass index (median in both groups is 27 kg/m^2; *P* = 0.40), but cases more often had a first-degree relative with prostate cancer (18% *versus* 11%; *P* = 0.11), less often had a higher education (college degree in 30% *versus* 38%; *P* = 0.06), and more often had been a farmer than controls (38% *versus* 25%; *P* = 0.05).

Table 1 shows dietary antioxidant intake for cases and controls. Lycopene intake was significantly lower in cases than in controls. The dietary intake of vitamin C, vitamin E, and β-carotene was slightly lower in cases than in controls. These differences are not statistically significant.

Estimated genotype and allele frequencies, and the main effects of the *XRCC1* genotypes on prostate cancer risk are shown in Table 2. All of the distributions were consistent with Hardy-Weinberg equilibrium. The number of black subjects was too small to study this group separately. Genotypic distributions in blacks and whites were comparable, and when we combined the data on blacks and whites (adjusted for age and ethnicity), the results were comparable with the results of whites only.

Variant allele frequencies for the codons 194 (9%) and 280

(5%) were too low to allow meaningful analyses, considering our small sample size. Men who had one or two copies of the 399*Gln* allele appeared to have a somewhat lower prostate cancer risk than men who were homozygous for the 399*Arg* allele. Conversely, we could say that being homozygous for the more common *Arg* allele is associated with a slightly increased risk (OR = 1.3; 95% CI, 0.8–2.2).

Combined Effect of XRCC1 Codon 399 Genotype and Dietary Intake. For this analysis, the *Arg/Gln* genotype and the *Gln/Gln* genotype are labeled "low-risk genotypes," whereas the *Arg/Arg* men are labeled as the "high-risk genotype." Table 2 shows the results of the joint analysis of the effects of the codon 399 genotype and dietary antioxidant intake. The division between low and high dietary antioxidant intake was based on the median values for the controls as presented in Table 1. Men with the *Arg/Arg* (high-risk) genotype appeared to have a small increased prostate cancer risk compared with those with the *Arg/Gln* or *Gln/Gln* genotype, which was remarkably consistent across all strata of dietary antioxidant intake. The prostate cancer risk for men with the *Arg/Arg* genotype and low vitamin E intake was higher than expected on the basis of absence of interaction on a multiplicative scale [observed: OR = 2.4; 95% CI, 1.0–5.6 and expected: OR = 1.2 (1.0 × 1.2)]. The test for interaction was not statistically significant (*P* = 0.30). Similarly, the *Arg/Arg* genotype in combination with low lycopene intake gave a slightly higher prostate cancer risk than expected on the basis of the independent effects (observed: OR = 2.0; 95% CI, 0.8–4.9 and expected: OR = 1.1). Again, the test for interaction was not statistically significant (*P* = 0.31).

In this pilot study we could not find evidence that a higher intake of several types of dietary fats (total fat, saturated fat, oleic acid, and linoleic acid) was related to prostate cancer risk. Nor was there evidence that genotype modulated risk from dietary fat.

Some prostate cancer risk factors are related to increased tumor stage. In our study, 27 cases were diagnosed with tumors classified as TNM stage I, 44 cases had a higher stage tumor, and 6 were unknown. Restriction of analysis to higher-stage cases (TNM stage II or higher) did not substantially alter the results.

Discussion

We proposed a hypothesis that low antioxidant intake puts men at higher risk of prostate cancer if they have reduced BER capacity relative to men with normal repair.

Several avenues are available to evaluate this hypothesis. Ideally, direct measures of BER capacity could be used and compared between cases and controls. An example of this is an *in vitro* BER assay described recently, in which mammalian cell extracts (55) were tested for their ability to repair a single lesion at a defined position in a plasmid substrate. With this assay several steps in the BER process can be evaluated by examining the repair of specific oxidized bases, such as 8-oxo-7,8-dihydroguanine, and sites of base loss (abasic sites). Another useful system for assessing the repair activity of a cell extract for reconstituting repair from its components is the comet assay or single cell gel electrophoresis (56). A ROS-inducing agent, such as H_2O_2 or ionizing radiation, can be used to damage the cells, and the kinetics of cellular repair can be monitored.

An important difficulty in using these assays in case-control designs is that they may be affected by cancer status. Tumor burden might decrease repair capacity through high

Table 2 Associations of *XRCC1* polymorphisms with prostate cancer

Genotype	Cases (*n* = 76) No. (%)	Controls (*n* = 182) No. (%)	OR adjusted[a] (95% CI)	*P*
Codon 194				
Arg/Arg	67 (88)	152 (84)	1	
Arg/Trp	9 (12)	28 (15)	0.8 (0.4–1.8)	0.56
Trp/Trp	0 (0)	2 (1)	ND[b]	ND[b]
Arg/Arg	67 (88)	152 (84)	1	
Arg/Trp + *Trp/Trp*	9 (12)	30 (16)	0.7 (0.3–1.6)	0.45
Allele frequency *Trp*	5.9%	8.8%		
Codon 280				
Arg/Arg	66 (87)	164 (90)	1	
Arg/His	10 (13)	18 (10)	1.5 (0.7–3.6)	0.31
His/His	0 (0)	0 (0)		
Allele frequency *His*	6.6%	4.9%		
Codon 399				
Arg/Arg	37 (49)	77 (42)	1	
Arg/Gln	30 (39)	78 (43)	0.8 (0.5–1.4)	0.45
Gln/Gln	9 (12)	27 (15)	0.7 (0.3–1.6)	0.38
Arg/Arg	37 (49)	77 (42)	1	
Arg/Gln + *Gln/Gln*	39 (51)	105 (58)	0.8 (0.5–1.3)	0.34
Allele frequency *Gln*	31.6%	36.3%		

[a] Adjusted for age and ethnicity.
[b] ND, not defined, because of zero counts in one cell.

Table 3 Associations of *XRCC1* codon 399 genotype and dietary antioxidant intake[a] with prostate cancer, combined analysis

Dietary intake of[b]	*XRCC1* codon 399 genotype					
	Arg/Gln + *Gln/Gln*			*Arg/Arg*		
	No. of cases/ no. of controls	OR[c] (95% CI)	*P*	No. of cases/ no. of controls	OR[c] (95% CI)	*P*
Vitamin C						
high	15/49	1 (ref)		14/41	1.4 (0.5–3.4)	0.51
low	24/54	1.4 (0.6–3.4)	0.43	24/36	2.3 (0.9–5.8)	0.06
Vitamin E						
high	17/46	1 (ref)		14/44	1.0 (0.4–2.6)	0.93
low	22/57	1.2 (0.5–2.8)	0.65	24/33	2.4 (1.0–5.6)	0.04
Vitamin A						
high	20/53	1 (ref)		21/37	1.7 (0.8–3.9)	0.20
low	19/50	0.6 (0.2–1.5)	0.26	17/40	0.8 (0.3–2.2)	0.69
β-Carotene						
high	20/52	1 (ref)		18/38	1.4 (0.6–3.2)	0.46
low	19/51	0.7 (0.3–1.9)	0.54	20/39	1.3 (0.5–3.2)	0.57
Lycopene						
high	15/45	1 (ref)		14/45	1.1 (0.4–2.6)	0.91
low	24/58	1.0 (0.4–2.4)	0.98	24/32	2.0 (0.8–4.9)	0.13

[a] Values adjusted for energy intake according to regression method of Willett and Stampfer (54).
[b] Dietary antioxidant intake: high and low are above and below the median in the control group, see Table 1.
[c] Adjusted for age, ethnicity, first degree relative with prostate cancer, education, ever been a farmer, BMI, total energy intake, total fat intake, and intake of the other antioxidants.

metabolic rate and excessive endogenously generated oxidative stress, which might affect lymphocytes and their repair values (57). A nested case-control or case-cohort design with prospective BER capacity measurements would avoid this problem.

The use of genotype data is an appealing alternative to functional measures, because genotype does not change with disease state. In addition, genotyping assays have fewer sample requirements and lower costs than repair capacity assays. The *XRCC1* codon 399 polymorphism has been studied in relation to several cancer types other than prostate cancer, with various results, some finding increased risks for the *Gln* allele (42, 43, 45, 46) but others finding an increased risk for the *Arg* allele

(47, 58, 59). Possibly, genotypic effects may be different for different types of cancer. The 399*Gln* allele has shown association with increased levels of DNA damage, such as aflatoxin B_1 DNA adducts (53), somatic glycophorin A variants (53), sister chromatid exchange frequencies (60), and higher levels of detectable DNA adducts (61). However, these *in vitro* assays using placental cells and peripheral blood cells are not specifically targeted at oxidative damage and may not be representative of the ability of cells to cope with oxidative damage *in vivo*.

Direct measures of the effect of *XRCC1* codon 399 polymorphisms on repair of oxidative damage are still lacking.

Convincing demonstrations could involve comparison of BER in isogenic cell lines where *XRCC1* has been knocked out, and either the *Arg* or the *Gln* allele has been restored and is constitutively expressed. Alternatively, one could determine BER capacity in many men with different *XRCC1* genotypes to see if capacity correlated with genotype. In addition, it would be useful to study the DNA repair genotype in relation to specific oxidative markers including urinary excretion of oxidized bases and direct measures of oxidative damage in DNA extracted from target tissue or surrogate cells, such as lymphocytes (62).

Genotype studies should not be limited to a single player in the BER pathway. Integrating information on allelic variants of other genes in the pathway at the same time is important to obtain a broader view on the functioning of the BER pathway. Examples are polymorphisms in the 8-oxoguanine DNA glycosylase (*hOGG1*), and apurinic endonuclease (*APE*) genes. Several polymorphisms have been identified in the *hOGG1* gene that have been shown to reduce the activity of the enzyme *in vitro* (63–65). One study found that levels of the oxidative DNA lesion 8-hydroxy-2′-deoxyguanosine in normal lung tissue DNA of subjects with lung cancer were not associated with constitutive *hOGG1* genotype (66). Recently, however, two of the polymorphisms have been shown to be significantly related to prostate cancer risk (67). The functional significance of polymorphisms in the *APE* gene is not clear yet and they have not been examined in relation to prostate cancer. However, the gene may be interesting because it has been found to be expressed more strongly in prostate cancer and prostatic intraepithelial neoplasia than in benign prostate hypertrophy (68). Furthermore, an integrative study of polymorphisms in genes involved in the detoxification of ROS (*i.e.,* GST gene family) and repair of ROS-induced DNA damage may help identify those individuals at the highest cancer risk.

Similar to the use of BER repair capacity assays, it is also important to ensure that dietary intake has not been influenced by cancer status. The effect of dietary intake on prostate cancer risk would be best studied using a nested case-control or case-cohort design in which prospective dietary information is available. Furthermore, prediagnostic plasma levels of antioxidants would provide better estimation of antioxidant status than questionnaire data, taking into account not only the consumption, but also the absorption and utilization of the antioxidants.

Furthermore, for sufficient power to examine interaction between dietary antioxidants and BER capacity in prostate cancer risk future studies need to much larger than this one. Large studies would also provide finer or continuous classification of dietary intake, whereas the small sample size in our study allowed only dichotomization of antioxidant intake, limiting the interpretability of our results.

Although preliminary and limited because of small sample size, the results of our pilot study suggest that the increased prostate cancer risk from the *Arg* allele of *XRCC1* was greatest among men with low intake of the antioxidants vitamin E and lycopene. If future studies are able to confirm our hypothesis, it would suggest that a simple dietary intervention of increased intake of vitamin E and lycopene can be used to overcome the increased prostate cancer risk associated with an inherited DNA repair gene polymorphism.

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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

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