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Polymorphisms in *NFKB1* and *NFKBIA* Genes Modulate the Risk of Developing Prostate Cancer among Han Chinese

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Background: Nuclear factor kappa B (NF-κB) pathway proteins play an important role in modulating inflammation and other carcinogenic processes. Polymorphisms within NF-κB pathway genes may influence cancer risk. This study aimed to examine the association between *NFKB1*9-4 ATTG ins→del, *NFKBIA* 3' UTR A→G, -826CT and -881AG polymorphisms and prostate cancer risk among Chinese.

Material/Methods: The polymorphisms were genotyped via PCR-RFLP technique on 936 prostate cancer patients and 936 population-based healthy controls. Logistic regression model was used to measure the risk association present.

Results: With the exception of *NFKBIA* 3' UTR polymorphism, the heterozygous and mutant genotypes of the other polymorphisms were significantly associated with prostate cancer risk. For *NFKB1* polymorphism, a decreased risk was observed, with adjusted OR: 0.69; 95% CI: 0.44, 0.98; P=0.01 (heterozygous) and adjusted OR: 0.60; 95% CI: 0.37, 0.91; P=0.02 (mutant). *NFKBIA* -826CT and -881AG polymorphisms were in complete linkage disequilibrium and shared the same risk association, with adjusted OR: 1.34; 95% CI: 1.09, 1.62; P=0.02 (heterozygous) and adjusted OR: 2.83; 95% CI: 1.79, 4.50; P=0.01 (mutants). Interestingly, the impact of the *NFKB1* polymorphism was not present in nonsmokers and younger (<60 years) subjects (P<0.05).

Conclusions: In conclusion, polymorphisms in *NFKB1* and *NFKBIA* genes may modulate the risk of developing prostate cancer among Chinese.

MeSH Keywords: Asian Continental Ancestry Group • Association • Genetic Association Studies • Genotype • Polymorphism, Genetic

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Background

Prostate cancer is a common type of cancer in men, with an estimated annual incidence of 238,590 cases [1]. Although most of the prostate cancer cases happen in the developed countries, recent years have witnessed the rapid increase in prostate cancer incidence in developing populations, including China [2]. Prostate cancer is also one of the leading causes of cancer-related mortality, accounting for 10% of all male cancer-related deaths, in both Western and Asian populations [3]. Considering the significance of the disease, there is a pressing need for identifying risk factors of prostate cancer, so that the disease can be detected at an early stage, which facilitates prostate cancer treatment and management.

The mechanism of prostate carcinogenesis is extremely complicated. However, it has been generally accepted that the etiology of prostate cancer is influenced by several factors such as smoking habits, age, ethnicity, and, importantly, genetic factors [4–6]. It has been shown previously that the latter could contribute to up to 42% of prostate cancer risk [6]. Candidate gene association study (CGAS) is an established method for identifying genetic variants associated with a disease [7]. The approach focuses only on genes that could be of relevance to the mechanism of the disease of interest [7,8]. The specific polymorphisms that could either affect gene expression or the protein product of the chosen candidate genes were then selected. Subsequently, the frequencies of the polymorphic genotypes were compared between subjects with and without the disease, and statistical models were used to determine risk association [7,8].

Many studies on prostate carcinogenesis have focused on the role of genetic factors that mediate inflammatory response [9–12], as inflammation has been extensively linked to the etiology of prostate cancer, although other mechanisms such as cell adhesion also plays an important role [13,14]. Given the important role of inflammation in carcinogenesis, the present candidate gene association study focused on genes relevant to inflammation. Among all the proteins involved in inflammatory response, the nuclear factor-kappa B (NF-κB) pathway proteins, notably p50 (NF-κB1) and its critical inhibitor, IκBα, appeared to have the most important function. NF-κB activation can lead to the synthesis of several enzymes, including inducible nitric oxide synthase (iNOS) and cyclooxygenase-2, which catalyze the release of reactive oxygen species that damages adjacent cells. The NF-κB pathway has also been shown to regulate the production of many pro-inflammatory cytokines, such as TGF-β, TNF-α, IL-6, and IL-8, which further supports the role of NF-κB in inflammation. Inflammation causes various genomic lesions to the cells, which facilitates cancer development. Additionally, improper activation of NF-κB1 can cause enhanced cell proliferation and evasion of apoptosis, which are 2 of the cancer hallmarks. Therefore, under normal conditions, NF-κB1 is bound to IκBα inhibitor when its expression is not needed.

NF-κB1 and IκBα are encoded by *NFKB1* and *NFKBIA* genes, respectively. The impact of polymorphisms within the *NFKB1* and *NFKBIA* genes on cancer risk has been extensively investigated in a number of cancers [15–21], but surprisingly few studies have been performed on prostate cancer [22,23]. The risk modulation effects of the polymorphisms were inconsistent in different studies, which could be because of the small sample sizes recruited and the ethnic background differences of subjects in different studies. The present study aimed to examine the association of *NFKB1* 9-4 ATTG ins→del, *NFKBIA* 3' untranslated region (UTR) A→G, -826CT and -881AG polymorphisms with risk of developing prostate cancer among Chinese in a large sample size.

Material and Methods

Subjects

Between September 2008 and June 2014, 936 newly diagnosed, histopathologically confirmed sporadic prostate cancer patients were randomly recruited from the First Affiliated Hospital of Bengbu Medical College, Bengbu Third People's Hospital, the Second Affiliated Hospital of Bengbu Medical College, the People's Liberation Army 123rd Hospital China and Bengbu First People's Hospital. Based on medical records, patients who had family history of prostate cancer and those who suffered from malignancies other than prostate cancer were excluded. Healthy males (N=936) were randomly recruited from the general population as controls. Controls were matched with patients by age (±5 years). The age of the patients recruited ranged from 50 to 76 years old, with a mean of 62.0±6.89 years. The controls' ages ranged from 48 to 73 years old, with a mean of 61.4±7.11. Based on our previous preliminary findings (data not shown), the peak age of prostate cancer incidence in our population occurred at 60 years old. Therefore, subjects below 60 years old were categorized as "young", while those 60 years or above were categorized as "old" in our analysis. 442 of the patients and 389 of the controls were smokers, while the rest were nonsmokers. Information on the subjects' age was collected based on the medical registration form (which was in turn based on the official identity card of the People's Republic of China). On the other hand, information on the smoking habits was obtained from an interview with subjects on recruitment. All subjects were self-described ethnic Han Chinese. They were asked to sign a written informed consent before donating 3 ml blood for genetic analysis. The study was approved by the Medical Ethics Board (MEB) of Bengbu Medical College (approval no. BMC/1/IMO/2008.0415504).

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Table 1. Frequency of *NFKB1* and *NFKBIA* genotypes.

SNP/genotype	Patient	Control	*P* value	HWE *P* value (case + control)*
NFKB1			0.03**	0.94
Ins/ins	63	38		
Ins/Del	339	331		
Del/del	534	567		
NFKBIA 3' UTR			0.58	0.55
AA	173	165		
AG	442	458		
GG	321	313		
NFKBIA -826CT			<0.01**	0.78
CC	508	586		
CT	356	321		
TT	72	29		
NFKBIA -881AG			<0.01**	0.78
AA	508	586		
AG	356	321		
GG	72	29		

* HWE – Hardy-Weinberg Equilibrium; ** significant at P<0.05.

Genotyping of polymorphisms

DNA was extracted from blood samples by using the TIANGEN DNA Purification Kit. All polymorphisms were genotyped by previously described PCR-RFLP technique (NFKB1, [15]; NFKBIA 3' UTR [21], NFKBIA -826CT, and -881AG [19]), with the researchers blinded to the case/control status of the samples. For *NFKB1* polymorphism, the PCR primers were TGGGCACAAGTCGTTTATGA (forward) and CTGGAGCCGGTAGGGAAG (reverse), while the restriction enzyme used was PflMI (Van91I). For *NFKBIA* 3' UTR polymorphism, the PCR primers were GGCTGAAAGAACATGGACTTG (forward) and GTACACCATTTACAGGAGGG (reverse), while HaeIII was used for the digesting the PCR products. *NFKBIA* -826CT and -881AG polymorphisms were amplified simultaneously by using GGTCCTTAAGGTCCAATCG (forward) and GTTGTGGATACCTTGCACTA (reverse). *NFKBIA* -826CT polymorphism was digested by using BfaI, and *NFKBIA* -881AG polymorphism was digested by using TspRI. Approximately 10% of randomly selected samples were sequenced to confirm the genotypes.

Statistical analysis

All analyses were performed by using SPSS version 17.0. Continuous variables were assessed by using the independent samples t-test and are presented as mean ±SD. Categorical variables were tested by using the chi-square test. The Hardy-Weinberg equilibrium was analyzed by using a goodness-of-fit chi-square test. An unconditional logistic regression model was performed to calculate the odds ratios (ORs) and their corresponding 95% confidence intervals (95% CI) to assess the association of the polymorphisms with prostate cancer risk. The overall ORs were also adjusted to age and smoking status of the subjects. A p-value <0.05 was statistically significant.

Results

Frequency of *NFKB1* and *NFKBIA* genotypes

The frequency of *NFKB1* and *NFKBIA* genotypes in the 936 patients and 936 controls are shown in Table 1. Significant differences in

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Table 2. Association of the SNPs and prostate cancer risk.

SNP/Genotype	Patient	Control	Odds ratio (95% CI)*	*P* value
NFKB1				
Ins/ins	63	38	–	–
Ins/Del	339	331	0.69 (0.44–0.98)	0.01**
Del/del	534	567	0.60 (0.37–0.91)	0.02**
NFKBIA 3' UTR				
AA	173	165	–	–
AG	442	458	0.90 (0.69–1.22)	0.61
GG	321	313	0.94 (0.68–1.32)	0.84
NFKBIA -826CT				
CC	508	586	–	–
CT	356	321	1.34 (1.09–1.62)	0.02**
TT	72	29	2.83 (1.79–4.50)	0.01**
NFKBIA -881AG				
AA	508	586	–	–
AG	356	321	1.34 (1.09–1.62)	0.02**
GG	72	29	2.83 (1.79–4.50)	0.01**

* Adjusted to age and smoking status; ** significant at P<0.05.

genotype frequency were observed between patients and controls for the *NFKB1*9-4 ATTG polymorphism (P=0.03), *NFKBIA* -826CT polymorphism (P<0.01), and *NFKBIA* -881AG polymorphism (P<0.01). The frequency for *NFKBIA* -826CT and -881AG polymorphisms was identical, indicating the presence of linkage disequilibrium (LD). In addition, the genotype frequency for all the polymorphisms followed Hardy-Weinberg Equilibrium (Table 1).

Association of the SNPs and prostate cancer risk

Table 2 showed the association of the SNPs and prostate cancer risk. Significant association was found for *NFKB1*9-4 ATTG, *NFKBIA* -826CT and -881AG polymorphisms, but not the *NFKBIA* 3' UTR polymorphism. For *NFKB1*9-4 ATTG polymorphism, the ins/del genotype and del/del genotype were associated with a lower prostate cancer risk, with adjusted OR: 0.69; 95% CI: 0.44, 0.98; P=0.01 and adjusted OR: 0.60; 95% CI: 0.37, 0.91; P=0.02 respectively. For *NFKBIA* -826CT and -881AG polymorphisms, a higher prostate cancer risk association was observed. Since both polymorphisms were in LD, they had an identical risk value, with adjusted OR: 1.34; 95% CI: 1.09, 1.62; P=0.02 for heterozygotes and adjusted OR: 2.83; 95% CI: 1.79, 4.50; P=0.01 for mutants.

Combined effect of *NFKB1* and *NFKBIA* polymorphisms

Significant polymorphisms were evaluated for their combined effect on prostate cancer risk. The results are shown in Table 3. With the exceptions of NFKB19–4 ATTG ins/ins + NFKBIA mutant and NFKB19-4 ATTG ins/del + NFKBIA mutant combinative genotypes, all other genotypes were significantly associated with a lower prostate cancer risk (OR<1.00) (Table 3).

Association of the SNPs and prostate cancer risk in people with different smoking status

The association above was analyzed separately for smokers and nonsmokers. The result is shown in Table 4. For smokers, similar to the overall findings described above, significant association with prostate cancer risk was observed for *NFKB1*9-4 ATTG, *NFKBIA* -826CT, and -881AG polymorphisms. However, for nonsmokers, the association of *NFKB1* polymorphism was absent, and only *NFKBIA* -826CT and -881AG polymorphisms showed risk association.

For smokers, the del/del genotype of *NFKB1*9-4 ATTG polymorphism was associated with a lower prostate cancer risk, with

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Table 3. Combined effect of the SNPs and prostate cancer risk.

SNP/genotype*	Patient	Control	Odds ratio (95% CI)	*P* value
NFKB1 + *NFKBIA*				
Ins/ins + WT	35	16	–	–
Ins/Del + WT	186	186	0.46 (0.24–0.85)	0.01**
Del/del + WT	285	306	0.42 (0.23–0.79)	0.01**
Ins/ins + Het	22	28	0.36 (0.16–0.81)	0.01**
Ins/Del + Het	127	119	0.49 (0.26–0.93)	0.03**
Del/del + Het	207	219	0.43 (0.23–0.80)	0.01**
Ins/ins + Mut	6	4	0.69 (0.17–2.77)	0.60
Ins/Del + Mut	26	26	0.46 (0.20–1.02)	0.06
Del/del + Mut	40	42	0.44 (0.21–0.91)	0.03**

* WT – CC for -826 polymorphism, AA for -881 polymorphism; Het – CT for -826 polymorphism, AG for -881 polymorphism; Mut – TT for -826 polymorphism, GG for -881 polymorphism; ** significant at P<0.05.

OR: 0.42; 95% CI: 0.22, 0.80; P<0.01, while the mutant genotypes of the *NFKBIA* -826CT and -881AG polymorphisms were associated with a higher prostate cancer risk, with OR: 2.78; 95% CI: 1.46, 5.31; P<0.01. For nonsmokers, *NFKBIA* -826CT and -881AG polymorphisms showed a higher risk association for prostate cancer in heterozygotes and mutants, with OR: 1.38; 95% CI: 1.07, 1.78; P=0.01 for heterozygotes and OR: 3.24; 95% CI: 1.75, 6.02; P<0.01 for mutants.

Association of the SNPs and prostate cancer risk in older and younger subjects

We also analyzed the association based on the age of the subjects (old *vs.* young). Table 5 shows the association of the SNPs and prostate cancer risk in older and younger subjects. The finding based on age was similar to the finding based on the smoking status above, such that for older subjects, an association was observed for *NFKB1*9-4 ATTG, *NFKBIA* -826CT, and -881AG polymorphisms, but for younger subjects the *NFKB1*9-4 ATTG association was lost.

For older subjects, the del/del genotype of *NFKB1*9-4 ATTG polymorphism was associated with a lower prostate cancer risk, with OR: 0.57; 95% CI: 0.32, 0.99; P=0.05. In contrast, *NFKBIA* -826CT and -881AG polymorphisms showed a higher risk association for prostate cancer in heterozygotes and mutants, with OR: 1.33; 95% CI: 1.02, 1.72; P=0.03 for heterozygotes and OR: 2.98; 95% CI: 1.67, 5.33; P<0.01 for mutants. However, in younger subjects, only the mutant genotypes of *NFKBIA* -826CT and -881AG polymorphisms were associated with prostate cancer risk, with OR: 2.69; 95% CI: 1.34, 5.42; P=0.01.

Discussion

NF-κB pathway proteins play an important role in modulating inflammation and other related cellular processes. Among the many NF-κB pathway proteins, the most abundant p50 (NF-κB1) has been thought to have the most important function in these cellular processes [24–26]. Regulation of p50 (NF-κB1) by its natural inhibitor, IκBα, is necessary for the former to carry out its cellular functions. The p50 (NF-κB1) and IκBα proteins were encoded by *NFKB1* and *NFKBIA* genes, respectively. Polymorphisms within these genes may alter their protein products in several ways, which in turn lead to differential cancer risk. Many studies have been performed to investigate the association of *NFKB1*9-4 ATTG ins→del, *NFKBIA* 3' UTR A→G, -826CT and -881AG polymorphisms and risk of various cancers [15-21]. However, surprisingly little research was performed on prostate cancers. Only 2 previous studies reported on the association of *NFKB1*9-4 ATTG ins→del polymorphism and prostate cancer risk [22,23], and no study has focused on *NFKBIA* polymorphisms. Moreover, the results from the 2 *NFKB1* reports contradicted one another. It is generally accepted that polymorphisms present different risk in people with different ethnic background, and that small sample sizes may cause misleading interpretation of results. These factors motivated us to perform the present study in a large sample size among Han Chinese. In this study, we excluded patients who had family history of prostate cancer because familial cancers are usually (but not always) caused by mutations in high-penetrance genes, which are rare in the general population. The present study aimed to identify low-penetrance susceptibility alleles, which, despite having modest risk modification effect, are very common in the general population. Patients

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Table 4. Association of the SNPs and prostate cancer risk in people with different smoking status.

Smoking status	SNP/genotype	Patient	Control	Odds ratio (95% CI)	*P* value
Smokers	*NFKB1*				
	Ins/ins	**31**	**14**	–	–
	Ins/Del	155	130	0.54 (0.27–1.06)	0.07
	Del/del	226	245	0.42 (0.22–0.80)	<0.01*
	NFKBIA 3' UTR				
	AA	68	77	–	–
	AG	207	184	1.27 (0.89–1.87)	0.21
	GG	137	128	1.21 (0.81–1.82)	0.35
	NFKBIA -826CT				
	CC	213	237	–	–
	CT	164	138	1.32 (0.99–1.77)	0.06
	TT	35	14	2.78 (1.46–5.31)	<0.01*
	NFKBIA -881AG				
	AA	213	237	–	–
	AG	164	138	1.32 (0.99–1.77)	0.06
	GG	35	14	2.78 (1.46–5.31)	<0.01*
Nonsmokers	*NFKB1*				
	Ins/ins	32	24	–	–
	Ins/Del	184	201	0.69 (0.40–1.21)	0.19
	Del/del	308	322	0.72 (0.41–1.25)	0.24
	NFKBIA 3' UTR				
	AA	105	88	–	–
	AG	235	274	0.72 (0.52–1.01)	0.05
	GG	184	185	0.83 (0.59–1.18)	0.31
	NFKBIA -826CT				
	CC	295	388	–	–
	CT	192	183	1.38 (1.07–1.78)	0.01*
	TT	37	15	3.24 (1.75–6.02)	<0.01*
	NFKBIA -881AG				
	AA	295	388	–	–
	AG	192	183	1.38 (1.07–1.78)	0.01*
	GG	37	15	3.24 (1.75–6.02)	<0.01*

* Significant at P<0.05.

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Table 5. Association of the SNPs and prostate cancer risk in older and younger subjects.

Smoking status	SNP/genotype	Patient	Control	Odds ratio (95% CI)	P value
Old	*NFKB1*				
	Ins/ins	36	21	–	–
	Ins/Del	186	184	0.59 (0.33–1.05)	0.07
	Del/del	302	311	0.57 (0.32–0.99)	0.05*
	NFKBIA 3' UTR				
	AA	100	88	–	–
	AG	224	256	0.77 (0.55–1.08)	0.13
	GG	180	172	0.92 (0.65–1.31)	0.65
	NFKBIA -826CT				
	CC	288	332	–	–
	CT	192	167	1.33 (1.02–1.72)	0.03*
	TT	44	17	2.98 (1.67–5.33)	<0.01*
	NFKBIA -881AG				
	AA	288	332	–	–
	AG	192	167	1.33 (1.02–1.72)	0.03*
	GG	44	17	2.98 (1.67–5.33)	<0.01*
Young	*NFKB1*				
	Ins/ins	25	17	–	–
	Ins/Del6	155	147	0.72 (0.37–1.38)	0.32
	Del/del	232	256	0.62 (0.32–1.17)	0.14
	NFKBIA 3' UTR				
	AA	73	77	–	–
	AG	198	202	1.03 (0.71–1.50)	0.86
	GG	141	141	1.05 (0.71–1.57)	0.79
	NFKBIA -826CT				
	CC	220	254	–	–
	CT	164	154	1.23 (0.93–1.63)	0.15
	TT	28	12	2.69 (1.34–5.42)	0.01*
	NFKBIA -881AG				
	AA	220	254	–	–
	AG	164	154	1.23 (0.93–1.63)	0.15
	GG	28	12	2.69 (1.34–5.42)	0.01*

* Significant at P<0.05.

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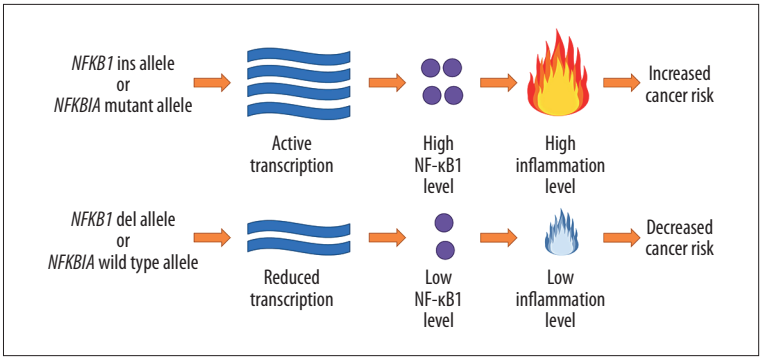

Figure 1. Potential mechanism by which *NFKB1* and *NFKBIA* polymorphisms mediate risk of prostate cancer.

who had malignancies other than prostate cancer were also excluded to prevent misidentification of susceptibility alleles associated with other cancers.

It has been well-established that many inflammatory-related cytokines, such as TGF-β, TNF-α, IL-6, and IL-8, mediate inflammation in the prostate through the NF-κB pathway [22,27–30]. Therefore, genes in the NF-κB pathway, notably *NFKB1* and *NFKBIA*, potentially play a role in prostate carcinogenesis. We showed that *NFKB1*9-4 ATTG ins→del, and *NFKBIA* -826CT and -881AG polymorphisms were associated with prostate cancer risk. We postulate that the polymorphisms modulate prostate cancer risk in our subjects by altering the transcription of the genes, since the polymorphisms were all located in the promoter region. For *NFKB1*9-4 ATTG polymorphism, the del allele was associated with a reduced prostate cancer risk. *In vitro* functional assay has shown that the del allele could decrease the level of transcription by approximately 2-fold [31]. This in turn reduces the protein translation, resulting in a lower production of p50 (NF-κB1) (Figure 1). Since p50 (NF-κB1) plays a role in inflammation, subjects who had less of the protein (i.e., those who carried the del allele) had a reduced level of inflammation. Considering that inflammation is positively linked to prostate carcinogenesis [9–12], subjects having the del allele were associated with a decreased prostate cancer risk, which explains our observation in this study. On the other hand, for the *NFKBIA* polymorphisms, we showed that the mutant allele was associated with an increased prostate cancer risk. It has been shown previously that the mutant allele can retard the transcription of the gene [32]. This retardation could lead to aberrant *NFKB1* expression, which results in an increased prostate cancer risk, as observed in our study (Figure 1).

We also found that all combinative genotypes of *NFKB1*9-4 ATTG ins→del and NFKBIA -881/-826 polymorphisms were significantly associated with prostate cancer risk, except the *NFKB1*9-4 ATTG ins/ins + *NFKBIA* mutant and *NFKB1*9-4 ATTG ins/del + NFKBIA mutant genotypes. The lack of significance of these 2 combinative genotypes could be caused by the small sample size included. It is interesting to note that all other combinative genotypes led to a reduced prostate cancer risk, which is in accordance to the effect of *NFKB1*9-4 ATTG polymorphism but not the *NFKBIA* polymorphisms. This suggests that the effect of *NFKB1*9-4 ATTG polymorphism was stronger than that of the *NFKBIA* polymorphisms. This observation was not unexpected, since the product of *NFKB1* plays a direct role in mediating inflammation, whereas that of *NFKBIA* plays an indirect role by regulating *NFKB1* expression.

There were several strengths and limitations in this study. The greatest strength was the large sample size. The combined sample size of the only 2 available studies on NF-κB pathway gene polymorphism was 487 prostate cancer patients and 513 controls [22,23]. The present study alone involved 936 prostate cancer patients and 936 controls, which had a much higher statistical power than the other 2 studies combined. Another strength of this study was that we analyzed not only the overall effect of the polymorphism on prostate cancer risk, but also the effect in smokers *vs.* nonsmokers and older *vs.* younger subjects. Both smoking habits and age have been established as strong risk factors for prostate cancer [4,5]. Therefore, separate analysis of the effect of the polymorphisms on subjects with different smoking habits and age was important to control the potential confounding factors. However, our study also had a limitation. We analyzed only a few polymorphisms in the NF-κB pathway. There are several other polymorphisms that could potentially modulate prostate cancer risk. However, only 4 were included in our study because we anticipated the significance of these 4 polymorphisms based on our literature review.

Conclusions

The del allele of the *NFKB1*9-4 ATTG polymorphism was associated with a decreased prostate cancer risk, while the mutant allele of *NFKBIA* -826CT and -881AG polymorphisms was associated with an increased prostate cancer risk. There have been very few studies investigating the association of NF-κB pathway gene polymorphism and prostate cancer risk. Therefore, this study adds valuable information to the currently available literature on the role of these polymorphisms on prostate cancer risk.

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Statement

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