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Original Article

The Cell Cycle Checkpoint Gene, *RAD17 rs1045051*, Is Associated with Prostate Cancer Risk

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Human RAD17, as an agonist of checkpoint signaling, plays an essential role in mediating DNA damage. This hospital-based case-control study aimed to explore the association between RAD17 rs1045051, a missense single nucleotide polymorphism (SNP), and prostate cancer risk. Subjects were 358 prostate cancer patients and 314 cancer-free urology patients undergoing treatment at the Zhujiang Hospital of Southern Medical University in China. RAD17 gene polymorphism rs1045051 was evaluated by the SNaPshot method. Compared with the RAD17 gene polymorphism rs1045051 AA genotype, there was a higher risk of prostate cancer for the CC genotype (adjusted odds ratio [AOR] = 1.731, 95% confidence interval [95%CI] = 1.031–2.908, $p = 0.038$). Compared with the A allele, the C allele was significantly associated with the disease status (AOR = 1.302, 95%CI = 1.037–1.634, $p = 0.023$). All these findings indicate that in the SNP rs1045051, both the CC genotype and C allele may have a substantial influence on the prostate cancer risk.

Key words: prostate cancer, single-nucleotide polymorphisms, cell cycle checkpoint, rs1045051, RAD17

Prostate cancer is one of the most common male cancers [1], and its incidence has steadily increased, especially in recent years [2]. Certain genetic mutations, either alone or in combination, have been shown to play essential roles in the progression of prostate cancer [3-5]. Therefore, elucidation of the mechanism of the gene damage-related response in prostate cells would be of great significance in preventing prostate cancer progression [6].

The cell cycle checkpoint is the main pathway regulating cell cycle transitions. Previous studies have suggested that checkpoints can arrest the cell cycle to provide sufficient time for activating damage-repair genes that work to repair the DNA damages generated during gene replication [7]. Cell cycle checkpoint loss not only results in genomic instability, but more importantly, it can increase the risk of mutation, leading to malignant tumors [7, 8]. The subtle genetic changes due to functional polymorphisms in cell cycle-related genes can compound the genetic risk of cancer development [9].

RAD17, which is encoded by Schizosaccharomyces pombe, is one of the cell cycle checkpoint proteins that function to mediate DNA damage during replication disruption [10]. Recent studies have shown that RAD17

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is essential for sustained cell growth, maintenance of chromosomal stability and ATR-dependent checkpoint activation upon DNA damage [11,12]. In addition, RAD17 has also been shown to act as a sensor of DNA replication progression and may be involved in homologous recombination [13].

Single nucleotide polymorphisms (SNPs) are DNA sequence polymorphisms caused by DNA point mutations that give rise to different alleles, and are the most common type of genetic variation in humans. SNPs that present in the coding region (coding SNPs) result in a change of amino acid, which may be associated with the risk of developing particular diseases [14]. SNPs of DNA mismatch repair (MMR) system genes have been found to be associated with tumorigenesis in various cancers [6]. SNPs in the genes of this system may affect gene function, gene expression, and the effectiveness of gene-related systems [10,15,16]. These findings suggest that the susceptibility of an individual to a particular cancer may be related to their genotype. This principle would also be applicable to RAD17, as recent studies have revealed that in certain Schizosaccharomyces pombe RAD17-deleted strains, the expression of RAD17 may result in an inhibition of yeast colony growth and retardation of the cell cycle progression [17].

Some studies have revealed an association between RAD17 rs1045051 and the risks of esophageal squamous cell carcinoma and colorectal cancer [18,19]. However, associations between specific SNPs and prostate cancer have not yet been elucidated. In this study, we aimed to investigate the genotype frequencies of the RAD17 SNP in a Chinese population and to explore the influence of this SNP on the risk of prostate cancer.

Materials and Methods

Ethical approval. All procedures involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The protocol was approved by the Ethics Committee of Zhujiang Hospital, Southern Medical University.

Study subjects. The 672 subjects were patients at the Department of Urology, Zhujiang Hospital, Guangzhou in China between January 2015 and April 2018, and consisted of 358 patients who were diagnosed with histologically confirmed prostate cancer and 314 cancer-free urology patients. In this study, tumor stage was determined according to the UICC TNM (Unio Internationalis Contra Cancrum Tumor-Node-Metastasis) classification. Informed consent was obtained from the enrolled subjects after a detailed description of the study. The study was approved by the ethics committee of the Zhujiang Hospital of Southern Medical University.

In the stratification analysis, localized and advanced prostate cancer were classified according to the following criteria: for localized prostate cancer, T1-2 N0M0, Gleason score of 2-7, and PSA levels ≤ 50 ng/mL; for advanced prostate cancer, T3-4, N+ or M+, Gleason score of 8-10, and PSA levels > 50 ng/mL. Gleason grading was performed by experienced pathologists based on the 2018 EUA Guidelines. TNM staging was determined by postoperative pathologic presentation or according to imaging studies and biopsy reports.

The control group comprised 314 cancer-free men who were confirmed to be free of prostate cancer based on PSA levels or rectal examination. Control subjects whose total PSA was persistently above 4 ng/mL underwent a prostate biopsy to eliminate the possibility of prostate cancer.

Blood collection, DNA extraction and genotyping. A 2-ml aliquot of peripheral blood was collected from each subject. Samples were stored in vacuum tubes containing EDTA at −20°C (or −80°C for samples stored longer than 1 month). Genomic DNA was extracted using a TIANamp Blood DNA Kit (Tiangen Biotech, Beijing) according to the manufacturer's instructions, and was quantified to ensure that sufficient DNA could be extracted for the subsequent genotyping. Genotyping and analyses of the RAD17 gene polymorphism rs1045051 were performed by the Life Technologies Corporation (Shanghai, China) using an ABI SNaPshot® multiplex system.

Multiplex PCR (first PCR). SNaPshot processing of genomic DNA was performed at the Zhujiang Hospital of Southern Medical University. Multiplex PCR amplification was conducted using a MyCycler™ Thermal Cycler, with a template based on 1 μL genomic DNA (10-50 ng), 2.5 μL 10 × PCR buffer (Mg^{2+} free), 50 mM $MgCI_2$, 2.5 mM of each dNTP, 0.2 μL Platinum® Taq (5 U/μL), and 1 μL first primer mix, with ddH_2O added to a final reaction volume of 25 μL. The program started with a denaturation step of 95°C for 5 min followed by 33 cycles of 95°C for 30 sec, 56°C

for 30 sec and 72°C for 30 sec, with a final extension step for 5 min at 72°C. The first PCR primers for RAD17 gene polymorphism rs1045051 were as follows: upper primer, 5'-ACGTTGGATGGGCAGCAAAAGC ACTTTTTC-3'; lower primer, 5'-ACGTTGGATGAT CCAGCCTGGACAGTAGAGAC-3'.

The examination of PCR products was performed on 2% agarose gel. Prior to genotyping, primers and dNTPs that were not involved in the reaction were removed from the initial PCR process to prevent their overreaction in the subsequent extension reactions. A 2 μL aliquot of the PCR product was incubated for 90 min at 37°C in a system that contained 0.3 μL of shrimp alkaline phosphatase (SAP, 1 U/μL), 0.2 μL of Exo I(20 U/μL) and 7.5 μL of ddH_2O, followed by enzyme inactivation for 15 min at 75°C.

SNaPshot reaction. The typing primer provided for RAD17 gene polymorphism rs1045051 was 5'-TTT TTTTTTTTTTTTTTGGCAATAGCTGAGTTT GG-3'. 1 μL of the purified products from the first PCR as a template, 1.5 μL of reaction mixture, and 0.5 μL of Probe Mix was prepared for the SNaPshot reactions. Reactions were conducted in the MyCycler™ Thermal Cycler under a protocol of 25 cycles at 96°C for 10 sec, 5°C for 5 sec and 60°C for 30 sec. A 0.3 μL aliquot of SAP (1 U/μL) was then treated for 1 h at 37°C followed by heat-inactivation for 15 min at 75°C to remove the excess ddNTPs.

Then in an ABI optical plate, 8.8 μL of Hi-Di™ formamide, 0.2 μL of Genescan™ 120 LIZ™ Size Standard and 1 μL of reaction mixture were combined, and denatured for 5 min at 95°C. The electrophoresis results from the ABI PRISM 3730 DNA Analyzer were analyzed using GeneMapper software ver. 4.1.

Statistical analysis. The deviation of genotype distribution from Hardy-Weinberg equilibrium was checked by Chi-square (χ^2) test. The allele and genotype data were analyzed based on a reference group of common allele homozygotes. Student's *t*-test was used for continuous variables and chi-square test was used for categorical variables to assess differences in the frequency distribution of clinical variables. The odds ratio (OR), adjusted odd ratio (AOR), 95% confidence interval (95%CI) and *p* values for the association between prostate cancer risk and genotypes (or alleles) were calculated by logistic regression analysis.

In stratification analyses, the age at diagnosis (≤ 70 and > 70 years) and the tumor aggressiveness (both the localized and advanced cases) were further estimated as stratification factors, respectively. The statistical data were adjusted for age (at time of diagnosis), smoking and alcohol consumption status during all the processes of analyses. All statistical analyses were performed with SPSS 22.0 software (IBM SPSS Statistics; IBM, Somers, NY, USA) and *p* values of < 0.05 were regarded to be statistically significant (two-tailed).

Results

Clinical characteristics. The clinical characteristics of the 672 male Chinese subjects (358 prostate cancer patients and 314 controls) are shown in Table 1. The mean age at diagnosis of cancer patients and mean age at inclusion of control subjects were 70.9 and 70.2 years, respectively. The genotype frequency of RAD17 gene polymorphism rs1045051 in the control group maintained Hardy-Weinberg equilibrium ($p = 0.917$). The allele and genotype frequencies of RAD17 gene polymorphism rs1045051 among cases and control subjects are listed in Table 2.

SNP analysis of RAD17 in prostate cancer. The percentage of prostate cancer patients with the RAD17 gene polymorphism rs1045051 C allele was 37.2%, vs. 31.2% for control subjects (Table 2). The percentages of prostate cancer patients and control subjects with the RAD17 gene polymorphism rs1045051 AA genotype were 39.1% and 46.8%, while the percentages for the CC genotype were 13.4% and 9.2%, respectively.

Compared with the AA genotype, the CC genotype increased the risk of prostate cancer (OR = 1.738, 95%CI: 1.038−2.911, $p = 0.036$ and AOR = 1.731, 95%CI: 1.031−2.908, $p = 0.038$). The AC/CC genotypes were also related to a higher risk of prostate cancer (OR = 1.371, 95%CI: 1.008−1.863, p=0. 044 and AOR=1. 374, 95%CI: 1. 010−1. 870, $p = 0.043$). In addition, the C allele had a statistically significant association with the A allele of RAD17 rs1045051 ($p = 0.022$).

SNP analysis of RAD17 in localized and advanced prostate cancer. In stratified analysis, patients were classified into a localized disease group and advanced disease group based on the aggressiveness of the prostate cancer (Table 3). In the localized disease group (the subjects were all cancer-free patients or healthy men), the CC genotype of RAD17 gene polymorphism rs1045051 still increased the prostate cancer risk compared with the AA genotype (AOR = 2.423, 95%CI:

Table 1 Demographic and clinical characteristics of study subjects

Variables	Controls	Cases	Localized PCa	Advanced PCa	*P* value*
No. of subjects	314	358	128	230	
Mean age (SD)	70.2 (9.9)	70.9 (9.1)	71.3 (8.9)	70.7 (9.2)	0.358
Mean PSA (SD)	2.8 (1.3)	37.4 (78.8)	24.7 (36.5)	44.5 (93.8)	**0.000**
Smoking status No. (%)					0.594
Never	220 (70.1)	244 (68.2)	85 (66.4)	159 (69.1)	
Ever	94 (29.9)	114 (31.8)	43 (33.6)	71 (30.9)	
Drinking status No. (%)					0.283
Never	261 (83.1)	286 (79.9)	104 (81.3)	182 (79.1)	
Ever	53 (16.9)	72 (20.1)	24 (18.7)	48 (20.9)	
Gleason score					
No. of subjects (%)		347	120	227	
2–6		80 (23.1)	51 (42.5)	29 (12.8)	
7		118 (34.0)	60 (50.0)	58 (25.5)	
8–10		149 (42.9)	9 (7.5)	140 (61.7)	
Tumor stage#					
No. (%)		344	119	225	
T1		42 (12.2)	30 (25.2)	12 (5.4)	
T2		142 (41.3)	81 (68.1)	61 (27.1)	
T3		117 (34.0)	6 (5.0)	111 (49.3)	
T4		43 (12.5)	2 (1.7)	41 (18.2)	
Nodal stage					
No. (%)		317	117	200	
N0		239 (75.4)	114 (97.4)	125 (62.5)	
N1		78 (24.6)	3 (2.6)	75 (37.5)	
Metastasis stage					
No. (%)		342	118	224	
M0		238 (69.6)	116 (98.3)	122 (54.5)	
M1		104 (30.4)	2 (1.7)	102 (45.5)	

*Calculated *p* values based on data from control subjects and all case subjects.
#Tumor stage according to the UICC TNM classification.
PCa, prostate cancer; SD, standard deviation; PSA, Prostate-specific antigen.

Table 2 Comparison of genotype frequencies of RAD17 gene polymorphism rs1045051

SNP	Genotype or Allele	Controls (n=314) No. (%)	Cases (n=358) No. (%)	Crude OR (95% CI)	*P* value	Adjusted* OR (95% CI)	*P* value
rs1045051	AA	147 (46.8)	140 (39.1)	1.000 [Ref.]		1.000 [Ref.]	
	AC	138 (44.0)	170 (47.5)	1.293 (0.937–1.786)	0.118	1.296 (0.936–1.794)	0.118
	CC	29 (9.2)	48 (13.4)	1.738 (1.038–2.911)	0.036	1.731 (1.031–2.908)	**0.038**
	AC/CC	167 (53.2)	218 (60.9)	1.371 (1.008–1.863)	0.044	1.374 (1.010–1.870)	**0.043**
	A	432 (68.8)	450 (62.8)	1.000 [Ref.]		1.000 [Ref.]	
	C	196 (31.2)	266 (37.2)	1.303 (1.038–1.635)	0.022	1.302 (1.037–1.634)	**0.023**

*Adjusted for age, smoking status and drinking status in a logistic regression model.
SNP, single-nucleotide polymorphisms; OR, Odds Ratio; 95% CI, 95% confidential interval.

1.286–4.566, $p=0.006$). The C allele was found to confer an increased risk of prostate cancer compared to the A allele of RAD17 rs1045051 (AOR=1.464, 95%CI: 1.081–1.982, $p=0.014$). However, there was no significant association between RAD17 rs1045051 and the prostate cancer risk in the advanced group.

SNP analysis of RAD17 for ages at diagnosis (≤70 or >70 years). In another stratified analysis, the

Table 3 RAD17 gene polymorphism rs1045051 genotype and allele frequencies [n (%)] and adjusted OR stratified by aggressiveness

Genotype or allele	Controls (n=314)	Localized cases (n=128)	Adjusted* OR (95% CI)	*P* value	Controls (n=314)	Advanced cases (n=230)	Adjusted* OR (95% CI)	*P* value
AA	147 (46.8)	50 (39.1)			147 (46.8)	90 (39.1)		
AC	138 (44.0)	54 (42.2)	1.171 (0.745–1.841)	0.494	138 (44.0)	116 (50.5)	1.365 (0.950–1.963)	0.093
CC	29 (9.2)	24 (18.7)	2.423 (1.286–4.566)	**0.006**	29 (9.2)	24 (10.4)	1.351 (0.738–2.472)	0.329
AC/CC	167 (53.2)	78 (60.9)	1.395 (0.916–2.124)	0.121	167 (53.2)	140 (60.9)	1.363 (0.963–1.927)	0.080
A	432 (68.8)	154 (60.2)	1.00 (Ref.)		432 (68.8)	296 (64.3)	1.00 (Ref.)	
C	196 (31.2)	102 (39.8)	1.464 (1.081–1.982)	**0.014**	196 (31.2)	164 (35.7)	1.219 (0.944–1.573)	0.129

*Adjusted for age, smoking and drinking status in a logistic regression model.
OR, Odds Ratio; 95% CI, 95% confidential interval.

Table 4 RAD17 gene polymorphism rs1045051 genotype and allele frequencies [n (%)] and adjusted OR stratified by age at diagnosis

Genotype or allele	Age at diagnosis ≤70				Age at diagnosis >70			
	Controls (n=138)	Cases (n=159)	Adjusted* OR (95% CI)	*P* value	Controls (n=176)	Cases (n=199)	Adjusted* OR (95% CI)	*P* value
AA	65 (47.1)	60 (37.7)	1.00 (Ref.)		82 (46.6)	80 (40.2)	1.00 (Ref.)	
AC	62 (44.9)	85 (53.5)	1.523 (0.936–2.478)	0.090	76 (43.2)	85 (42.7)	1.129 (0.723–1.762)	0.594
CC	11 (8.0)	14 (8.8)	1.323 (0.552–3.170)	0.530	18 (10.2)	34 (17.1)	1.956 (1.018–3.755)	**0.044**
AC/CC	73 (52.9)	99 (62.3)	1.491 (0.933–2.381)	0.095	94 (53.4)	119 (59.8)	1.293 (0.854–1.960)	0.225
A	192 (69.6)	205 (64.5)	1.00 (Ref.)		240 (68.2)	245 (61.6)	1.00 (Ref.)	
C	84 (30.4)	113 (35.5)	1.258 (0.889–1.779)	0.194	112 (31.8)	153 (38.4)	1.338 (0.988–1.811)	0.060

*Adjusted for age, smoking and drinking status in a logistic regression model.
OR, Odds Ratio; 95% CI, 95% confidential interval.

diagnosis age of 70 years was chosen as the dividing line to yield similar numbers of older and younger cases (Table 4). The CC genotype in the group over 70 years was significantly associated with the risk of prostate cancer (AOR=1.956, 95%CI: 1.018–3.755, $p=0.044$).

SNP analysis of RAD17 for distinct environment exposure factors and clinical characteristics. Subjects with the AA genotype were significantly distinct from those with the non-AA genotype in terms of the PSA level at diagnosis (ng/mL) ($p=0.007$). However, in the analysis of the association between RAD17 gene polymorphism rs1045051 and clinical characteristics, there were no significant associations with aggressiveness of disease, Gleason scores, age at diagnosis, smoking status, or drinking status (Table 5).

Discussion

Cell cycle checkpoints are the biochemical pathways that restrain the cell cycle transition and induce cell death after stress [20]. Certain enforcements of cell cycle checkpoints, such as the cellular response to DNA damage, are essential for the maintenance of genomic integrity and are activated in the early stages of tumorigenesis [21].

Albujja *et al.* reviewed the studies associating SNPs with the occurrence and development of prostate cancer, and summarized the potential predictive biomarkers [22], while RAD17 rs1045051 was found to be associated with a risk of prostate cancer in this study. As shown in Fig. 1, when a missense mutation occurs, the original codon (CUC) mutates into a new codon (CGC), resulting in a change of the original amino acid (Leu) to Arg. But unlike in DNA point mutation, SNPs are defined as DNA variants detectable in more than 1% of the population [23]. Therefore, the missense mutation occurrence of RAD17 rs1045051 may lead to a change in protein functions and RAD17 signaling, and could further cause cell cycle dysregulation, which is frequently observed in tumor development.

RAD17 is a protein product encoded by Schizosaccharomyces pombe cell cycle checkpoint genes and is

Table 5 Association of RAD17 gene polymorphism rs1045051 with clinical characteristics

rs1045051	Aggressiveness of disease no. (%)		Gleason score [n (%)]			PSA level at diagnosis Mean (ng/mL)			Mean age (years) at diagnosis	Smoking status		Drinking status	
	Localized	Advanced	2–6	7	8–10	<4	4–10	>10		Never	Ever	Never	Ever
No. of subjects	128	230	80	118	149	260	182	230	70.6 (n=672)	464	208	547	125
Reference:	50	90	28	51	56	129	76	82	71.1	197	90	239	48
AA	(39.1)	(39.1)	(35.0)	(43.2)	(37.6)	(49.6)	(41.8)	(35.7)	(n=287)	(42.5)	(43.3)	(43.7)	(38.4)
Association:	78	140	52	67	93	131	106	148	70.2	267	118	308	77
AC/CC	(60.9)	(60.9)	(65.0)	(56.8)	(62.4)	(50.4)	(58.2)	(64.3)	(n=385)	(57.5)	(56.7)	(56.3)	(61.6)
P value	0.990			0.461			**0.007**		0.243	0.844		0.280	

PSA, prostate-specific antigen.

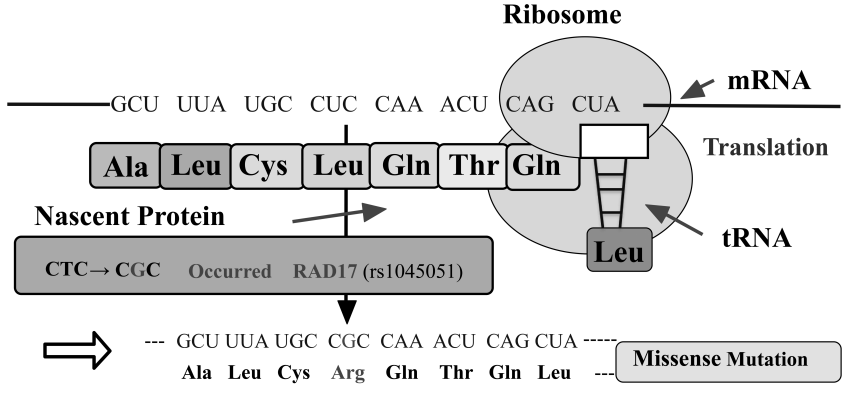

Fig. 1 The schema of RAD17 rs1045051 and missense mutation.

indispensable in checkpoint control pathways to cope with DNA damage and replication disruption [10]. RAD17 is essential for sustained cell growth, maintenance of chromosomal stability and ATR-dependent checkpoint activation upon DNA damage. RAD17 may also serve as a sensor of DNA replication progression and may be involved in homologous recombination. Meanwhile, RAD17 shares strong similarity with DNA replication factor C (RFC), and can form a complex with RFCs. RAD17 has a weak ATPase activity required for binding to chromatin, and recruits the RAD1-RAD9-HUS1 checkpoint protein complex and RHNO1 onto chromatin after DNA damage. In response to DNA damage, RAD17 can also be phosphorylated by the checkpoint kinase ATR. The P-loop (also called the Walker A motif), an indispensable region for the nucleotide binding of ATPase's, and the C terminus with two SQ motifs (Ser635 and Ser645), which are effective targets of ATR kinase, are the two essential regions of this protein [18]. The phosphorylation of these two SQ sites is required for the DNA-damage-induced cell cycle G2 arrest, and is thought to be a critical early event during checkpoint signaling in DNA-damaged cells. Another recent study reported that the interaction between RAD17-RFC2-5 and 9-1-1 complexes is also relevant to the ATR-Chk1 pathway, which is an important checkpoint pathway of DNA damage. And iVERGE, a conserved amino acid motif, at the C-terminal tail of RAD17 conserved the Y665 and S667 residues. The phosphorylation of the RAD17-S667 residue is significant for the interaction of RAD17 with the 9-1-1 complex, but the function of Y665 would depend on the phosphorylation of RAD17-S667, which means that iVERGE combines with manifold pathways to regulate ATR-Chk1 [24]. The results above show that there might be many direct or indirect links between RAD17 and DNA damage; our present experiments were designed to explore one of them.

In this case-control study, we specifically focused on RAD17 and the relation of its single nucleotide polymorphism, rs1045051, to prostate cancer incidence. We found that RAD17 rs1045051 was a risk factor for prostate cancer in this Chinese population, and certain mutations in RAD17 rs1045051 are possible genetic causes of prostate cancer. To our knowledge, our study is the first to report an association between RAD17 gene polymorphism rs1045051 and prostate cancer risk.

RAD17 has previously been reported as a genetic risk factor for other cancers. A link between RAD17

rs1045051 and the risk of esophageal squamous cell carcinoma was reported in a 2016 study of a Japanese population, and a 2017 study found an association between the RAD17 codon 546 polymorphism and the risk of colorectal cancer among Japanese [18, 19]. The Arg/Arg genotype of RAD17 rs1045051 was associated with higher risk of colorectal cancer in males [18]. In our study, the CC genotype conferred a higher risk of prostate cancer in men over the age of 70, and was also associated with an increased risk of localized prostate cancer. Based on the above evidence, we believe that RAD17 is inextricably linked to tumorigenesis.

In conclusion, the CC genotype and C allele in RAD17 gene polymorphism rs1045051 may have a substantial influence on prostate cancer risk. Our study suggests that RAD17 rs1045051 may be used as a new indicator for the diagnosis of prostate cancer or the prediction of treatment efficacy.

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