The impact of receptor of advanced glycation end-products polymorphisms on prostate cancer progression and clinicopathological characteristics

Ying-Erh Chou1,2,3 | Ming-Ju Hsieh4,5,6 | Shian-Shiang Wang1,7,8 | Chia-Yen Lin1,7 | Yen-Yu Chen9 | Yung-Chuan Ho3,9 | Shun-Fa Yang2,3

1School of Medicine, Chung Shan Medical University, Taichung, Taiwan
2Institute of Medicine, Chung Shan Medical University, Taichung, Taiwan
3Department of Medical Research, Chung Shan Medical University Hospital, Taichung, Taiwan
4Oral Cancer Research Center, Changhua Christian Hospital, Changhua, Taiwan
5College of Medicine, National Chung Hsing University, Taichung, Taiwan
6Graduate Institute of Biomedical Sciences, China Medical University, Taichung, Taiwan
7Division of Urology, Department of Surgery, Taichung Veterans General Hospital, Taichung, Taiwan
8Department of Applied Chemistry, National Chi Nan University, Nantou, Taiwan
9Department of Medical Applied Chemistry, Chung Shan Medical University, Taichung, Taiwan

Correspondence
Yung-Chuan Ho and Shun-Fa Yang, Department of Medical Research, Chung Shan Medical University Hospital, No. 110, Sec. 1, Jianguo N. Road, Taichung 402, Taiwan. Emails: ych065@csmu.edu.tw (Y-CH); ysf@csmu.edu.tw (S-FY)

Abstract
The receptor for advanced glycation end products (RAGE) overexpression was suggested to be associated with prostate cancer development and poor prognosis. In this study, we focused on the correlations between the clinicopathological characteristics and susceptibility of prostate cancer and RAGE single-nucleotide polymorphisms (SNPs). In 579 prostate cancer patients, the RAGE SNPs rs1800625, rs1800624, rs2070600 and rs184003 in patients with or without grade group upgrade were analysed with real-time polymerase chain reaction. The results demonstrated that the prostate cancer patients who carried the RAGE SNPs rs2070600 'GA' genotypic variants were significantly associated with lower risk to develop grade group upgrade. Moreover, patients with the RAGE rs1800625 'TC + CC' genotypic variants were associated with higher risk of perineural invasion. In 343 prostate cancer patients who carried the RAGE rs1800625 'TC + CC' genotype without grade group upgrade were correlated with higher risk of biochemical recurrence and perineural invasion. In the analysis of TCGA database, significant differences of the RAGE mRNA level were found between the normal controls and prostate cancer patients (p < 0.0001), and the pathologic stage N1 and N0 patients (p = 0.0027). The prostate cancer patients with high RAGE expression were associated with lower overall survival rate (p = 0.025). In conclusion, our results have revealed that the RAGE SNPs rs2070600 and rs1800625 were associated with the grade group upgrade of prostate cancer and clinical status. The RAGE polymorphisms may provide as a pivotal predictor to evaluate prostate cancer disease progression and prognosis.

KEYWORDS
polymorphism, prostate cancer, RAGE
1 | INTRODUCTION

Prostate cancer (PCA) is a global health problem with considerable diversity in epidemiology and genomics. In Taiwan, prostate cancer is the fifth most prevalent cancer and ranks the seventh highest cancer-related mortality rate. Epidemiological risk factors such as ageing and high fat consuming diet were suggested to raise the incidence of PCa in Taiwan. RAGE, or the AGER, is the receptor for advanced glycation end products (AGEs). The AGEs are non-enzymatic protein modifications, which were produced during ageing. In prostate cancer, overexpression of RAGE and its ligand amphoterin were found to be correlated with tumour development and poor prognosis. The RAGE expression was observed to be correlated with apoptosis induction and inhibition of prostate tumour growth, and the RAGE quantification of human prostate cancer samples has been confirmed that increased uptake of RAGE was corresponding to increasing of Gleason scoring.

The polymorphisms of RAGE were suggested to be associated with various cancers, including oral cancer, breast cancer, lung cancer, gastric cancer, hepatocellular carcinoma (HCC), pancreas cancer, cervical cancer, urothelial cell carcinoma and colorectal cancer. Previous studies revealed that the RAGE rs1800625 polymorphism was correlated with the increasing of cancer risk in various cancers including oral cancer and gastric cancer. Moreover, the ‘TT’ polymorphisms of rs184003 were suggested to be correlated with poorer disease-specific survival on urothelial cell carcinoma, and individuals who carried the rs184003 T allele were found to exhibit increased risk of breast cancer. However, the RAGE polymorphisms to prostate cancer progression and clinicopathologic characteristics remained not well-investigated. In this study, we focused on four SNPs of RAGE rs1800625, rs1800624, rs2070600 and rs184003, and try to elucidate their correlations to clinicopathologic characteristics and susceptibility of prostate cancer.

2 | MATERIALS AND METHODS

2.1 Study subjects

In the current study, 579 prostate cancer patients with adenocarcinoma were enrolled as the study group. During 2012–2017, the patients who involved in our study have received robotic assisted radical prostatectomy at Taichung Veteran General Hospital. The informed consent was confirmed and acquired from each individual who enrolled in our study (IRB No. CE19062A). The medical information including the age at diagnosis (years), initial PSA level at diagnosis (ng/ml), clinical and pathological TNM staging, pathologic Gleason grade group, perineural invasion, seminal vesicle invasion, lymphovascular invasion, biochemical recurrence and D’Amico classification was acquired from the personal medical records for each patient. Before this study started to initiate, the certification and approval was confirmed by the Institutional Review Board (IRB) of the Taichung Veteran General Hospital.

2.2 Sample preparation and DNA extraction

For genomic DNA extraction, the peripheral blood specimens from normal controls and prostate cancer patients who enrolled in our study were collected. The samples of peripheral whole blood were preserved in EDTA containing tubes and centrifuged with the settings of 3000 g for 10 min. The buffy coats extracted from centrifuged whole blood specimens were further applied for the DNA extraction.

| Variable | No (n = 343) | Yes (n = 236) | p Value |
|----------|-------------|-------------|---------|
| Age at diagnosis (years) | | | |
| <65 | 142 (41.4%) | 103 (43.6%) | 0.591 |
| >65 | 201 (58.6%) | 133 (56.4%) | |
| PSA at diagnosis (ng/ml) | | | |
| ≤10 | 156 (45.5%) | 114 (48.3%) | 0.503 |
| >10 | 187 (54.5%) | 122 (51.7%) | |
| Pathologic Gleason grade group | | | |
| 1 + 2 + 3 | 295 (86.0%) | 189 (80.1%) | 0.059 |
| 4 + 5 | 48 (14.0%) | 47 (19.9%) | |
| Pathologic T stage | | | |
| 1 + 2 | 284 (82.8%) | 217 (91.9%) | 0.002* |
| 3 + 4 | 59 (17.2%) | 19 (8.1%) | |
| Pathologic N stage | | | |
| N0 | 307 (89.5%) | 223 (94.5%) | 0.034* |
| N1 | 36 (10.5%) | 13 (5.5%) | |

**TABLE 1** The distributions of demographical characteristics in 579 patients with prostate cancer
and to complete the DNA elution. The final extracted DNA was prepared as DNA template in polymerase chain reactions (PCRs).

### 2.3 Selection of RAGE SNPs and RAGE SNPs genotyping

In our current study, a total of four SNPs of RAGE rs1800625, rs1800624, rs2070600 and rs184003 were selected from the International HapMap Project database. The RAGE rs1800624 polymorphism was suggested to contribute to increase breast cancer and lung cancer risk. The RAGE rs2070600 polymorphism was associated with significant breast cancer and gastric cancer risk. The assessment of allelic discrimination for the RAGE rs184003, rs2070600, rs1800624 and rs1800625 SNP was performed with ABI StepOne Software v2.3 Real-Time PCR System. The genotyping was analysed with the TaqMan assay. The SDS 7000 series software (Applied Biosystems) was applied for the analysis and calculation of the final data of genotyping.

### 2.4 Statistical analysis

To compare the age at diagnosis (years), PSA at diagnosis (ng/ml), clinical T stage, pathologic T stage, pathologic Gleason grade group, pathologic N stage, perineural invasion, seminal vesicle invasion, lymphovascular invasion, biochemical recurrence and D’Amico classification between the patients with or without grade group upgrade, Student’s t test and chi-squared test or was used between these two groups. A statistical significant was considered if \( p < 0.05 \). To evaluate the odds ratio (OR) with their 95% confidence intervals (CIs) of the association between the prostate cancer risk and the clinical pathological characteristics and genotypic frequencies, logistic regression models were adopted for data analysis and assessment. The analysis of all the data in our study was evaluated and calculated with SAS statistical software (Version 9.1, 2005; SAS Institute).

### 3 RESULTS

In 579 patients with prostate cancer, the distribution of demographic characteristics was demonstrated in Table 1. In our study, we found that the distributions of age at diagnosis (years) >65 of the patients with no grade group upgrade were 58.6% (201/343) and 56.4% (133/236) of the patients with grade group upgrade. The PSA at diagnosis >10 ng/ml between these two groups was 54.5% (187/343) and 51.7% (122/236), respectively. A statistical significant difference was found for clinical T stage \( (p = 0.002) \), pathologic N
stage \((p = 0.034)\) and D’Amico classification \((p = 0.001)\) between the prostate cancer patients with or without grade group upgrade (Table 1).

The distribution frequency of RAGE genotypes of 579 prostate cancer patients was listed in Table 2. The highest distribution frequencies in prostate cancer patients of RAGE polymorphisms rs1800625, rs1800624, rs2070600 and rs184003 were homozygous for TT, homozygous for TT, homozygous for GG and homozygous for GG, respectively. The odds ratios (ORs) and their 95% confidence intervals (CIs) were estimated by logistic regression models. After adjustment for the effects of age at diagnosis, PSA levels at diagnosis, clinical T stage, pathologic T stage, pathologic N stage, pathologic Gleason grade group, perineural invasion, seminal vesicle invasion, lymphovascular invasion, biochemical recurrence and D’Amico classification, a significant difference \((p = 0.019)\) and adjusted odds ratios (AORs) = 0.628 with CIs = 0.426–0.926 was observed in prostate cancer patients with or without grade group upgrade with RAGE rs2070600 ‘GA’ genotype compared with the wild-type (WT) ‘GG’ carriers (Table 2).

We further analysed the distribution frequency of RAGE genotype in 270 patients with prostate cancer with \(\text{PSA} \leq 10\). Statistical significant differences were found in patients who carried the RAGE rs2070600 ‘GA’ \((\text{AOR} = 0.304, 95\% \text{ CI} = 0.164–0.563; p < 0.001)\) and ‘GA + AA’ \((\text{AOR} = 0.375, 95\% \text{ CI} = 0.214–0.657; p = 0.001)\) genotype (Table 3). To clarify the role of RAGE genetic polymorphisms in prostate cancer progression, we analysed the clinical status and RAGE genotypic frequencies in 579 prostate cancer patients. The RAGE rs1800625 ‘TC + CC’ genotype was found to be significantly associated with higher risk of perineural invasion \((\text{OR} = 2.272, 95\% \text{ CI} = 1.267–4.074; p = 0.005)\) (Table 4). We further analysed the clinical status and RAGE rs1800625 genotypic frequencies in 343 patients with no grade group upgrade. The RAGE rs1800625 ‘TC + CC’ genotype was significantly associated with perineural invasion \((\text{OR} = 2.610, 95\% \text{ CI} = 1.185–5.749; p = 0.014)\) and biochemical recurrence \((\text{OR} = 1.843, 95\% \text{ CI} = 1.024–3.317; p = 0.039)\) in patients without grade group upgrade (Table 5). We further analyse the correlations between the RAGE mRNA level and prostate cancer with the TCGA database. Statistical significant differences of the RAGE mRNA level were found between normal controls and prostate cancer patients \((p < 0.0001, \text{Figure 1A})\), and pathologic stage N1 and N0 patients \((p = 0.0027, \text{Figure 1C})\). However, no significant differences of the RAGE mRNA expression between pathologic N0 stage and N1 stage were observed (Figure 1B). The prostate cancer patients who posses higher RAGE expression were correlated with lower overall survival rate \((\text{Log Rank} p = 0.025, \text{Figure 1D})\).
DISCUSSION

The correlations between the RAGE SNPs and prostate cancer were demonstrated in this study. The grouped Gleason score (GS) categories-grade groups were proposed by Johns Hopkins Hospital in 2013 and adopted officially at the 2014 International Society of Urologic Pathology (ISUP) Consensus meeting. The grade group (GG) was defined as GS ≤ 6 (GG1), GS3 + 4 (GG2), GS4 + 3 (GG3), GS8 (GG4) and GS ≥ 9 (GG5), and each individual GG has a presumed similar prognosis for each GS category. In our current study, most of the patients who developed GG upgrade were diagnosed as intermediate risk (45.3%) or high risk (48.7%) under D’Amico classification, suggesting a great proportion of GG2 to GG5 distribution to these patients with clinical T1 + T2 staging (91.9%) and pathologic N0 staging (94.5%) (Table 1).

We further examined the correlations between the RAGE SNPs and grade group upgrade of prostate cancer. The genotypic frequencies of each variable were presented in Table 4. The ORs and 95% CIs were estimated by logistic regression models. The p value < 0.05 was statistically significant.
In prostate cancer patients with the \textit{RAGE} SNPs rs2070600 'GA' genotype were associated with lower risk to develop grade group upgrade (AOR = 0.628, 95% CI = 0.426–0.976; \(p = 0.019\)) (Table 2). Notably, we found that in 270 prostate cancer patients whose prostate-specific antigen (PSA) \(\leq 10\), patients who carried the \textit{RAGE} SNPs rs2070600 'GA' genotype (AOR = 0.304, 95% CI = 0.164–0.563; \(p < 0.001\)) and 'GA + AA' polymorphic variants (AOR = 0.375, 95% CI = 0.214–0.657; \(p = 0.001\)) were associated with lower risk to develop grade group upgrade, respectively (Table 3).

Cancer. We found that in prostate cancer patients with the \textit{RAGE} SNPs rs2070600 'GA' genotype were associated with lower risk to develop grade group upgrade (AOR = 0.628, 95% CI = 0.426–0.976; \(p = 0.019\)) (Table 2). Notably, we found that in 270 prostate cancer patients whose prostate-specific antigen (PSA) \(\leq 10\), patients who carried the \textit{RAGE} SNPs rs2070600 'GA' genotype (AOR = 0.304, 95% CI = 0.164–0.563; \(p < 0.001\)) and 'GA + AA' polymorphic variants (AOR = 0.375, 95% CI = 0.214–0.657; \(p = 0.001\)) were associated with lower risk to develop grade group upgrade, respectively (Table 3).

The role of \textit{RAGE} rs2070600 polymorphisms to cancer risk or disease susceptibility and prognosis remained controversial. Most studies have linked the \textit{RAGE} rs2070600 polymorphic variant A allele with increased cancer risk and poor prognosis of disease,\(^{16,30,42,53}\) However, in a study of lung cancer, \textit{RAGE} was suggested to act as a tumour suppressor in lung cancer.

\begin{table}
\centering
\begin{tabular}{|l|c|c|c|c|}
\hline
Variable & Genotypic frequencies & & & \\
\hline
\textbf{rs1800625} & \textbf{TT} (\textit{N} = 287) & \textbf{TC + CC} (\textit{N} = 56) & \textbf{OR (95% CI)} & \textbf{p Value} \\
\hline
\textbf{Pathologic Gleason grade group} & & & & \\
1 + 2 + 3 & 249 (86.8%) & 46 (82.1%) & 1.00 & \textit{p} = 0.362 \\
4 + 5 & 38 (13.2%) & 10 (17.9%) & 1.424 & (0.663–3.059) \\
\hline
\textbf{Clinical T stage} & & & & \\
1 + 2 & 239 (83.3%) & 45 (80.4%) & 1.00 & \textit{p} = 0.597 \\
3 + 4 & 48 (16.7%) & 11 (19.6%) & 1.217 & (0.587–2.522) \\
\hline
\textbf{Pathologic T stage} & & & & \\
2 & 165 (57.5%) & 25 (44.6%) & 1.00 & \textit{p} = 0.077 \\
3 + 4 & 122 (42.5%) & 31 (55.4%) & 1.677 & (0.942–2.985) \\
\hline
\textbf{Pathologic N stage} & & & & \\
N0 & 257 (89.5%) & 50 (89.3%) & 1.00 & \textit{p} = 0.953 \\
N1 & 30 (10.5%) & 6 (10.7%) & 1.028 & (0.407–2.599) \\
\hline
\textbf{Seminal vesicle invasion} & & & & \\
No & 229 (79.8%) & 38 (67.9%) & 1.00 & \textit{p} = 0.058 \\
Yes & 58 (20.2%) & 18 (32.1%) & 1.870 & (0.996–3.513) \\
\hline
\textbf{Perineural invasion} & & & & \\
No & 87 (30.3%) & 8 (14.3%) & 1.00 & \textit{p} = 0.014* \\
Yes & 200 (69.7%) & 48 (85.7%) & 2.610 & (1.185–5.749) \\
\hline
\textbf{Lymphovascular invasion} & & & & \\
No & 238 (82.9%) & 46 (82.1%) & 1.00 & \textit{p} = 0.887 \\
Yes & 49 (17.1%) & 10 (17.9%) & 1.056 & (0.499–2.235) \\
\hline
\textbf{D'Amico classification} & & & & \\
Low/intermediate risk & 137 (47.7%) & 22 (39.3%) & 1.00 & \textit{p} = 0.246 \\
High risk & 150 (52.3%) & 34 (60.7%) & 1.412 & (0.787–2.532) \\
\hline
\textbf{Biochemical recurrence} & & & & \\
No & 204 (71.1%) & 32 (57.1%) & 1.00 & \textit{p} = 0.039* \\
Yes & 83 (28.9%) & 24 (42.9%) & 1.843 & (1.024–3.317) \\
\hline
\end{tabular}
\caption{Odds ratio (OR) and 95% confidence interval (CI) of clinical status and RAGE rs1800625 genotypic frequencies in 343 patients with no grade group upgrade}
\end{table}

\textit{Note}: The ORs with analysed by their 95% CIs were estimated by logistic regression models. \(\ast\) \textit{p value} < 0.05 as statistically significant.
development, and the variant A allele of rs2070600 was suggested to be associated with decreased expression of the tumour suppressor gene RAGE. Although the role of RAGE in cancer development remained controversial, it was suggested that the RAGE rs2070600 polymorphisms were associated with the regulation of soluble RAGE (sRAGE) levels. In a study focused on Dutch population, the CC genotype of SNP rs2070600 (Gly82Ser) was found to be strongly associated with higher sRAGE levels.

In gastric cancer, subjects who carried the rs2070600 AG genotype were observed to have a decreased ability to produce sRAGE.

In lung cancer, the serum sRAGE level was found to be decreased during lung cancer progression and could reflect decreased RAGE expression in tissue, suggesting that the serum sRAGE may be a pivotal diagnostic biomarker for lung cancer. Compared with these results, although we lack of the data of sRAGE in our current study, it can be proposed that the RAGE rs2070600 polymorphic variant A allele might be linked with decreased level of sRAGE in prostate cancer, thereby decreasing the risk to develop grade group upgrade in prostate cancer patients, especially in those grade group upgrade patients whose PSA ≤ 10 (Tables 2 and 3).

We further examined the correlations between the RAGE SNPs and clinical status of prostate cancer. Intriguingly, we found that although the RAGE rs1800625 polymorphisms were not associated with the grade group upgrade of prostate cancer (Tables 2 and 3), however, the RAGE rs1800625 genotypic variants ‘TC + CC’ were found to be significantly associated with perineural invasion of prostate cancer (p = 0.005, Table 4). Moreover, in 343 prostate cancer patients with no grade group upgrade, the RAGE rs1800625 polymorphic variants ‘TC + CC’ were also found to be associated with perineural invasion (p = 0.014) and biochemical recurrence (p = 0.039) (Table 5). The RAGE rs1800625 polymorphisms were suggested to be associated with increased cancer risk in various cancers. Previous study has suggested that the C allele of rs1800625 may induce the expression of RAGE, and leads to chronic inflammatory conditions in diabetic retinopathy. Besides, the variant of the RAGE rs1800625 SNP was suggested to be associated with the hypomethylation of the promoter region of RAGE and contribute to the ulcerative colitis risk.

Furthermore, after we analysed the TCGA database, we found that the RAGE mRNA level was significantly associated with prostate cancer tumorigenesis (Figure 1A) and pathologic N1 stage development (Figure 1C). The higher RAGE expression was also observed to be associated with lower overall survival rate in prostate cancer patients (Log Rank p = 0.025, Figure 1D). Moreover, Aboushousha et al. revealed that RAGE expression was significantly higher in prostate cancer lesions compared with prostatitis and benign prostatic hyperplasia. Taken together, it can be assumed that the RAGE rs1800625 polymorphic variants were associated with higher RAGE expression and tumour aggressiveness in prostate cancer development, leading to perineural invasion and biochemical recurrence in prostate cancer patients yet without grade group upgrade, and ultimately leads to poor prognosis and overall survival rate. However, future well-designed studies are required to elucidate the exact
mechanisms of RAGE SNPs in prostate cancer development, especially the influence of RAGE rs2070600 and rs1800625 SNPs to the sRAGE level regulation in prostate cancer tumour development and progression.

In conclusion, our results have demonstrated that the RAGE SNPs rs2070600 and rs1800625 were associated with prostate cancer grade group upgrade and tumour progression and prognosis. The prostate cancer patients who carried the RAGE rs2070600 allelic variant A allele were associated with lower risk to develop grade group upgrade, while the RAGE rs1800625 ‘TC + CC’ were associated with perineural invasion and biomedical recurrence in patients with no grade group upgrade. The RAGE rs1800625 might be linked with RAGE promoter hypomethylation and higher mRNA level in prostate cancer. The RAGE rs2070600 and rs1800625 polymorphisms may provide as pivotal markers to predict tumour aggressiveness, recurrence and prognosis in prostate cancer.

CONFLICTS OF INTEREST
The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTION
Ying-Erh Chou: Conceptualization (equal); Writing-original draft (equal); Writing-review & editing (equal). Ming-Ju Hsieh: Methodology (equal); Writing-original draft (equal). Shian-Shiang Wang: Resources (equal). Chia-Yen Lin: Resources (equal). Yen-Yu Chen: Methodology (equal). Yung-Chuan Ho: Conceptualization (equal); Writing-original draft (equal); Writing-review & editing (equal). Shun-Fa Yang: Conceptualization (equal); Writing-original draft (equal); Writing-review & editing (equal).

DATA AVAILABILITY STATEMENT
The data used to support the findings of this present study are available from the corresponding author upon request.

ORCID
Shun-Fa Yang https://orcid.org/0000-0002-0365-7927

REFERENCES
1. Zhu Y, Mo M, Wei YU, et al. Epidemiology and genomics of prostate cancer in Asian men. Nat Rev Urol. 2021;18(5):282-301.
2. Hung CF, Yang CK, Ou YC. Urologic cancer in Taiwan. Jpn J Clin Oncol. 2016;46(7):605-609.
3. Lin CY, Wang SS, Yang CK, et al. Genetic polymorphism and carboxy anhydrase 9 expression can predict nodal metastatic prostate cancer risk in patients with prostate-specific antigen levels ≤10 ng/ml at initial biopsy. Urol Oncol. 2019;37(11):814.e9-814.e16.
4. Wen Y-C, Lee W-J, Tan P, et al. By inhibiting snail signaling and miR-23a-3p, osthole suppresses the EMT-mediated metastatic ability in prostate cancer. Oncotarget. 2015;6(25):21120-21136.
5. Pu YS. Prostate cancer in Taiwan: epidemiology and risk factors. Int J Androl. 2000;23(Suppl 2):34-36.
6. Soman S, Raju R, Sandhya VK, et al. A multicellular signal transduction network of AGE/RAGE signaling. J Cell Commun Signal. 2013;7(1):19-23.
7. Bao JM, He MY, Liu YW, et al. AGE/RAGE/Akt pathway contributes to prostate cancer cell proliferation by promoting Rb phosphorylation and degradation. Am J Cancer Res. 2015;5(5):1741-1750.
8. Singh R, Barden A, Mori T, Bellin L. Advanced glycation end-products: a review. Diabetologia. 2001;44(2):129-146.
9. Ishiguro H, Nakaigawa N, Miyoshi Y, et al. Receptor for advanced glycation end products (RAGE) and its ligand, amphoterin are overexpressed and associated with prostate cancer development. Prostate. 2005;64(1):92-100.
10. Zhao CB, Bao JM, Lu YJ, et al. Co-expression of RAGE and HMGB1 is associated with cancer progression and poor patient outcome of prostate cancer. Am J Cancer Res. 2014;4(4):369-377.
11. Zhang J, Shao S, Han D, et al. High mobility group box 1 promotes the epithelial-to-mesenchymal transition in prostate cancer PC3 cells via the RAGE/NF-κappaB signaling pathway. Int J Oncol. 2018;53(2):659-671.
12. Elangovan I, Thirugnanam S, Chen A, et al. Targeting receptor for advanced glycation end products (RAGE) expression induces apoptosis and inhibits prostate tumor growth. Biochem Biophys Res Commun. 2012;417(4):1133-1138.
13. Konopka CJ, Wozniak M, Hedhli J, et al. Quantitative imaging of the receptor for advanced glycation end-products in prostate cancer. Eur J Nucl Med Mol Imaging. 2020;47(11):2562-2576.
14. Xia W, Xu Y, Mao Q, et al. Association of RAGE polymorphisms and cancer risk: a meta-analysis of 27 studies. Med Oncol. 2015;32(2):442.
15. Xu Y, Lu Z, Shen N, Wang X. Association of RAGE rs1800625 polymorphism and cancer risk: a meta-analysis of 18 case-control studies. Med Sci Monit. 2019;25:7026-7034.
16. Zhao DC, Lu HW, Huang ZH. Association between the receptor for advanced glycation end products gene polymorphisms and cancer risk: a systematic review and meta-analysis. J BUON. 2015;20(2):614-624.
17. Su S, Chien M, Lin C, Chen M, Yang S. RAGE gene polymorphism and environmental factor in the risk of oral cancer. J Dent Res. 2015;94(3):403-411.
18. Yue L, Zhang Q, He L, et al. Genetic predisposition of six well-defined polymorphisms in HMGB1/RAGE pathway to breast cancer in a large Han Chinese population. J Cell Mol Med. 2016;20(10):1966-1973.
19. Tesárová P, Kalousová M, Jáchymová M, et al. Receptor for advanced glycation end products (RAGE)–soluble form (sRAGE) and gene polymorphisms in patients with breast cancer. Cancer Invest. 2007;25(8):720-725.
20. Pan H, He L, Wang B, Niu W. The relationship between RAGE gene four common polymorphisms and breast cancer risk in northeastern Han Chinese. Sci Rep. 2014;4:4355.
21. Lee J, Choi J, Chung S, et al. Genetic predisposition of polymorphisms in HMGB1-related genes to breast cancer prognosis in Korean women. J Breast Cancer. 2017;20(1):27-34.
22. Hashemi M, Moazeni-roodi A, Arbabi F, et al. Genotyping of -374A/T, -429A/G, and 63 bp Ins/del polymorphisms of RAGE by rapid one-step hexaprimer amplification refractory mutation system polymerase chain reaction in breast cancer patients. Nucleos Nucleot Acid. 2012;31(5):401-410.
23. Zhang W, Deng X, Tang R, Wang H. Receptor for advanced glycation end-product rs1800624 polymorphism contributes to increase breast cancer risk: evidence from a meta-analysis. Medicine. 2020;99(44):e22775.
24. Feng LJ, Liu HL, Tan Q, Jin P. 374T/A polymorphism of the receptor for advanced glycation end products is associated with decreased risk of breast cancer in a Chinese population. Int J Clin Exp Med. 2015;8(6):10109-10113.
25. Pan H, Niu W, He L, et al. Contributory role of five common polymorphisms of RAGE and APE1 genes in lung cancer among Han Chinese. PLoS One. 2013;8(7):e69018.
26. Wang X, Cui E, Zeng H, et al. RAGE genetic polymorphisms are associated with risk, chemotherapy response and prognosis in patients with advanced NSCLC. PloS One. 2012;7(10):e43734.

27. Wang H, Li Y, Yu W, et al. Expression of the receptor for advanced glycation end-products and frequency of polymorphism in lung cancer. Oncol Lett. 2015;10(1):51-60.

28. Schenk S, Schraml P, Bendik I, Ludwig CU. A novel polymorphism in the promoter of the RAGE gene is associated with non-small cell lung cancer. Lung Cancer. 2001;32(1):7-12.

29. Hu D, Liu Q, Lin X, et al. Association of RAGE gene four single nucleotide polymorphisms with the risk, invasion, metastasis and overall survival of gastric cancer in Chinese. J Cancer. 2019;10(2):504-509.

30. Li T, Qin W, Liu Y, et al. Effect of RAGE gene polymorphisms and circulating sRAGE levels on susceptibility to gastric cancer: a case-control study. Cancer Cell Int. 2017;17:19.

31. Gu H, Yang L, Sun Q, et al. Gly82Ser polymorphism of the receptor for advanced glycation end products is associated with an increased risk of gastric cancer in a Chinese population. Clin Cancer Res. 2008;14(11):3627-3632.

32. Su S-C, Hsieh M-J, Chou Y-E, et al. Effects of RAGE gene polymorphisms on the risk and progression of hepatocellular carcinoma. Medicine. 2015;94(34):e1396.

33. Krechler T, Jáchymová M, Mestek O, et al. Soluble receptor for advanced glycation end-products (sRAGE) and polymorphisms of RAGE and glyoxalase I genes in patients with pancreas cancer. Clin Biochem. 2010;43(10-11):882-886.

34. Xu Q, Xue F, Yuan B, et al. The interaction between RAGE gene polymorphisms and HPV infection in determining the susceptibility of cervical cancer in a Chinese population. Cancer Biomark. 2012;11(4):147-153.

35. Lee C-Y, Ng S-C, Hsiao Y-H, et al. Impact of the receptor for advanced glycation end products on prostate cancer progression and clinicopathological characteristics. J Cell Mol Med. 2018;9(21):3886-3893.

36. Hung SC, Wang SS, Li JR, et al. Impact of RAGE polymorphisms on urothelial cell carcinoma clinicopathologic characteristics and long-term survival. Urol Oncol. 2019;37(9):573.e9-573.e17.

37. Bedoui SA, Barbirou M, Stayoussef M, et al. Identification of novel advanced glycation end products receptor gene variants associated with colorectal cancer in Tunisians: a case-control study. Gene. 2020;754:144893.

38. Hu J-C, Lin C-Y, Wang S-S, et al. Impact of H19 polymorphisms on prostate cancer clinicopathologic characteristics. Diagnostics. 2020;10(9):656.

39. Su SC, Hsieh MJ, Lin CW, et al. Impact of HOTAIR gene polymorphism and environmental risk on oral cancer. J Dent Res. 2018;97(6):717-724.

40. Chou Y-E, Yang P-J, Lin C-Y, et al. The impact of HMGB1 polymorphisms on prostate cancer progression and clinicopathological characteristics. Int J Environ Res Public Health. 2020;17(19):7247.

41. International HapMap C. The International HapMap Project. Nature. 2003;426(6968):789-796.

42. Yin NC, Lang XP, Wang XD, Liu W. AGER genetic polymorphisms increase risks of breast and lung cancers. Genet Mol Res. 2015;14(4):17767-17787.

43. Pierorazio PM, Walsh PC, Partin AW, Epstein JI. Prognostic Gleason grade grouping: data based on the modified Gleason scoring system. BJU Int. 2013;111(5):753-760.

44. Epstein JI, Egevad L, Amin MB, et al. The 2014 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma. Am J Surg Pathol. 2016;40(2):244-252.

45. Athanazio D, Gotto G, Shea-Budgell M, Yilmaz A, Trpkov K. Global Gleason grade groups in prostate cancer: concordance of biopsy and radical prostatectomy grades and predictors of upgrade and downgrade. Histopathology. 2017;70(7):1098-1106.

46. Humphrey PA, Moch H, Cubilla AL, Ulbright TM, Reuter VE. The 2016 WHO classification of tumours of the urinary system and male genital organs-part B: prostate and bladder tumours. Eur Urol. 2016;70(1):106-119.

47. Sood A, Jeong W, Dalela D, et al. Role of robot-assisted radical prostatectomy in the management of high-risk prostate cancer. Indian J Urol. 2014;30(4):410-417.

48. Preisser F, Cooperberg MR, Crook J, et al. Intermediate-risk prostate cancer: stratification and management. Eur Urol Oncol. 2020;3(3):270-280.

49. Gupta NP, Murugesan A, Kumar A, Yadav R. Analysis of outcome following robotic assisted radical prostatectomy for patients with high risk prostate cancer as per D’Amico classification. Indian J Urol. 2016;32(2):115-119.

50. Hernandez DJ, Nielsen ME, Han M, Partin AW. Contemporary evaluation of the D’Amico risk classification of prostate cancer. Urolgy. 2007;70(5):931-935.

51. Schifffmann J, Wenzel P, Salomon G, et al. Heterogeneity in D’Amico classification-based low-risk prostate cancer: differences in upgrading and upstaging according to active surveillance eligibility. Urol Oncol. 2015;33(7):329.e13-329.e19.

52. Borley N, Feneley MR. Prostate cancer: diagnosis and staging. Asian J Androl. 2009;11(1):74-80.

53. Wu S, Mao L, Li Y, et al. RAGE may act as a tumour suppressor to regulate lung cancer development. Gene. 2018;651:86-93.

54. Gaens KHJ, Ferreira I, van der Kallen CJH, et al. Association of polymorphism in the receptor for advanced glycation end products (RAGE) gene with circulating RAGE levels. J Clin Endocrinol Metab. 2009;94(12):5174-5180.

55. Jing R, Cui M, Wang J, Wang H. Receptor for advanced glycation end products (RAGE) soluble form (sRAGE): a new biomarker for lung cancer. Neoplasma. 2010;57(1):55-61.

56. Uloza V, Tamauskaite T, Vilkeviciute A, et al. Determination of SIRT1 rs12778366, FGFR2 rs2981582, STAT3 rs744166, and RAGE rs1800625 single gene polymorphisms in patients with laryngeal squamous cell carcinoma. Dis Markers. 2019;2019:3907232.

57. Chocholaty M, Jáchymová M, Schmidt M, et al. Polymorphisms of the receptor for advanced glycation end-products and glyoxalase I in patients with renal cancer. Tumour Biol. 2015;36(3):2121-2126.

58. Hudson BI, Stickland MH, Futers TS, Grant PJ. Effects of novel polymorphisms in the RAGE gene on transcriptional regulation and their association with diabetic retinopathy. Diabetes. 2001;50(6):1505-1511.

59. Wang J, Zhen Y, Zhou Y, et al. Promoter methylation cooperates with SNPs to modulate RAGE transcription and alter UC risk. Biochem Biophys Rep. 2019;17:17-22.

60. Aboushousha T, Lashen R, Abdelnaser K, et al. Comparative expression of RAGE and SOX2 in benign and malignant prostatic lesions. Asian Pac J Cancer Prev. 2019;20(2):615-620.

---

**How to cite this article:** Chou Y-E, Hsieh M-J, Wang S-S, et al. The impact of receptor of advanced glycation end-products polymorphisms on prostate cancer progression and clinicopathological characteristics. J Cell Mol Med. 2021;25:10761-10769. doi:10.1111/jcmm.17025