Associations of Genetic Polymorphisms of mTOR rs2295080 T/G and rs1883965 G/A with Susceptibility of Urinary System Cancers

Zhichao Min,1 Yuanyuan Mi,2 Zhiwei Lv,3 Yangyang Sun,4 Bowen Tang,3 Hao Wu,3 Ze Zhang,3 Hong Pan,5 Yujuan Zhang,5 Chao Lu,3 Li Zuo,3, and Lifeng Zhang3

1Department of Urology, The First People’s Hospital of Hangzhou Lin’an District, Hangzhou 310000, China
2Department of Urology, Affiliated Hospital of Jiangnan University, Wuxi 214000, China
3Department of Urology, The Affiliated Changzhou No. 2 People’s Hospital of Nanjing Medical University, 29 Xinglong Road, Changzhou 213003, China
4Department of Pathology, The Affiliated Changzhou No. 2 People’s Hospital of Nanjing Medical University, 29 Xinglong Road, Changzhou 213003, China
5Department of Operation Theatre, The Affiliated Changzhou No. 2 People’s Hospital of Nanjing Medical University, 29 Xinglong Road, Changzhou 213003, China

Correspondence should be addressed to Chao Lu; deerchaonew@126.com, Li Zuo; jiaomin0324@126.com, and Lifeng Zhang; nj-likky@163.com

Received 7 May 2021; Accepted 18 December 2021; Published 17 January 2022

Academic Editor: Silvia Angeletti

Copyright © 2022 Zhichao Min et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Background. Genetic polymorphisms in mammalian target of rapamycin (mTOR) signaling axis can influence the susceptibility of cancer. The relationship between mTOR gene variants rs2295080 T/G and rs1883965 G/A and the risk of cancer remains inconsistent. The present study is aimed at comprehensively investigating the association between mTOR polymorphisms and susceptibility to cancer.

Methods. We conducted a comprehensive assessment using odds ratios (ORs), corresponding 95% confidence intervals (CIs), and in silico tools to evaluate the effect of mTOR variations. Immunohistochemical staining (IHS) and GSEA analysis were used to investigate the expression of mTOR in urinary system cancer.

Results. The pooled analysis involved 22 case-control studies including 14,747 cancer patients and 16,399 controls. The rs2295080 T/G polymorphism was associated with the risk of cancer (G-allele versus T-allele, OR = 0.89, 95% CI = 0.80–0.98, P = 0.023; GT versus TT, OR = 0.88, 95% CI = 0.81–0.96, P = 0.004; GG+GT versus TT, OR = 0.87, 95% CI = 0.78–0.96, P = 0.008), especially for cancers of the urinary system, breast, and blood. Variation rs1883965 G/A was associated with cancer susceptibility, especially for digestive cancer. IHS analysis showed that mTOR was upregulated in prostate and bladder cancer. GSEA revealed that the insulin signaling pathway, lysine degradation pathway, and mTOR signaling pathway were enriched in the high mTOR expression group.

Conclusions. The mTOR rs2295080 T/G polymorphism may be associated with susceptibility of urinary cancer. The expression of mTOR is positively correlated with tumor malignancy in prostate cancer.

1. Introduction

Malignant tumors are a major global public health problem [1]. Over the past decades, cancer-related morbidity and mortality have increased. In 2015, there were approximately 4.2 million new cancer cases in China and 2.8 million cancer-related deaths [2]. By 2018, the number of new carcinoma cases was expected to exceed 4.3 million, with 2.9 million deaths due to carcinoma [3]. Tumors arise due to the interaction of multiple environmental and internal factors. The internal factors are mainly manifested as changes of immune status and endocrine disorders and genetic mutations of vital signal transduction pathways [4, 5]. In Homo sapiens, missing phosphatase and tensin homologs of the phosphoinositide 3-kinase (PI3K)/Akt/mTOR signal transduction pathway on chromosome 10 are often activated in various carcinomas. They are involved in different cellular processes that include cell proliferation, angiogenesis, and
Mutation of central gene in the mTOR pathway could affect protein transcription and change the capacity of this pathway, which may be vital in carcinogenesis [9–11].

The mTOR gene, also known as FKBP12 rapamycin-associated protein (FRAP), acts as an essential serine-threonine kinase in signal transduction and participates in the biological processes of cell cycle, survival, and autophagy.
The human mTOR gene comprises 59 exons and is located on chromosome 1p36.2 [15, 16]. The gene is approximately 156 kb in length and plays a central role in the PI3K/AKT/mTOR pathway [17, 18]. The aberrant regulation of the mTOR signal transduction pathway has been implicated in a wide spectrum of carcinomas [19, 20]. Abnormal expression of mTOR has been described in several types of cancers, including kidney renal clear cell carcinoma (KIRC), bladder cancer (BLCA), primary liver cancer, esophageal carcinoma, and colorectal adenocarcinoma [21–25]. The changes may be associated with single-nucleotide polymorphisms (SNPs) and genetic mutations in the human genome [26, 27].

Previous studies have evaluated the association of genetic variants of the mTOR gene with the susceptibility to cancer. Results of a meta-analysis that included five eligible studies indicated that the rs2295080 TT genotype was related to increased cancer risk, but not with poor clinical outcome [28]. Another meta-analysis based on nine studies published several years later revealed that the rs2295080 T/G variant was associated with an increased risk of leukemia and a decreased risk of genitourinary cancers [29]. The correlation between variants of rs2295080 T/G or rs1883965 G/A and cancer risk remain unclear [30–33].

The current study sought to identify all eligible case-control studies to comprehensively assess the association between mTOR variants rs2295080 T/G or rs1883965 G/A and susceptibility to cancer [30–49]. In silico tools and immunohistochemical staining (IHS) analysis were used to investigate the expression of mTOR in three main urinary system cancers.

2. Materials and Methods

2.1. Search Strategy. The PMC, Embase, Chinese National Knowledge Infrastructure, and Google Scholar databases were searched for potentially relevant published studies. The search terms were (“rs2295080” OR “rs1883965” OR “mTOR” OR “Mammalian target of rapamycin”) AND (“cancer” OR “tumor” OR “carcinoma”) AND (“mutant” OR “variant” OR “variation”). The most recent search update was 01 March 2021. In addition to the databases, we also screened qualified research by checking references from published articles.

2.2. Inclusion and Exclusion Criteria. Studies meeting the following criteria were included: (a) case-control or cohort studies addressing the association between the variation mTOR rs2295080 T/G or rs1883965 G/A and risk of cancer, (b) sufficient data of genotype frequencies to evaluate ORs and 95% CIs, and (c) articles written in English or other languages. The major exclusion criteria were as follows: (a) lack of a control group, (b) insufficient data to calculate ORs, and (c) no relevance to mTOR rs2295080 T/G or rs1883965 G/A variants and cancer risk.

2.3. Data Extraction. Study characteristics retrieved from eligible studies included the surname of the first author, publication date, origin of participants, type of cancer, source of control, ethnicity, gene distribution of mTOR polymorphisms, P value of Hardy-Weinberg equilibrium (HWE) in controls, and method of genotyping. In the stratification analysis, acute lymphoblastic leukemia and acute myeloid leukemia were classified as blood cancer. Urinary system tumors include BLCA, PRAD, and KIRC. Carcinomas of the digestive system included esophageal squamous cell carcinoma, gastric cancer, and colorectal cancer. The study included Asian populations and was divided into West Asian and East Asian groups.

2.4. Statistical Analyses. ORs and 95% CIs were used to evaluate the strength of association between the mTOR variants rs2295080 T/G or rs1883965 G/A and cancer susceptibility. For the rs2295080 T/G variation, allelic comparison refers to G-allele versus (vs.) T-allele. The heterozygous, homozygous, dominant, and recessive models represent GT vs. TT, GG vs. TT, GG+GT vs. TT, and GG vs. GT+TT. For the rs1883965 G/A variation, these five genetic models were A-allele vs. G-allele, AG vs. GG, AA vs. GG, AA+AG vs. GG, and AA and AG+GG. Heterogeneity of studies was investigated by the Q statistic test. P < 0.05 indicated statistical significance. A P value of heterogeneity < 0.05 indicated heterogeneity among the studies. A random effects model (DerSimonian and Laird) was conducted to calculate the ORs. Otherwise, a fixed effects model (Mantel–Haenszel) was performed. P value of HWE was evaluated by Fisher’s exact test. Subgroup analyses included the type of cancer, ethnicity, source of control, and genotype method. Begg’s funnel plot was adopted to evaluate publication bias. The reliability of the included case-control studies was assessed by sensitivity analysis. STATA 11.0 software (StataCorp, College Station, TX, USA) was used for all statistical analyses.

2.5. In Silico and IHS Analysis of mTOR. We utilized an online database to investigate the MAFs in global and
Table 2: Stratified analysis of mTOR rs2295080 T/G and rs1883965 G/A polymorphisms on cancer susceptibility.

| Variables | N | Case/control | OR (95% CI) | Phet | P | OR (95% CI) | Phet | P | OR (95% CI) | Phet | P | OR (95% CI) | Phet | P |
|-----------|---|--------------|-------------|------|---|-------------|------|---|-------------|------|---|-------------|------|---|
| rs2295080 T/G | | | | | | | | | | | | | | |
| Total | 18 | 10447/11979 | 0.89 (0.80-0.98) | <0.001 | 0.023 | 0.88 (0.81-0.96) | 0.004 | 0.004 | 0.84 (0.65-1.07) | <0.001 | 0.162 | 0.87 (0.78-0.96) | <0.001 | 0.008 | 0.88 (0.70-1.11) | <0.001 | 0.288 |
| Cancer type | | | | | | | | | | | | | | | |
| Urinary | 6 | 3738/4340 | 0.76 (0.62-0.94) | <0.001 | 0.010 | 0.77 (0.70-0.85) | 0.522 | <0.001 | 0.71 (0.44-1.17) | <0.001 | 0.178 | 0.74 (0.62-0.88) | 0.004 | 0.001 | 0.82 (0.53-1.27) | <0.001 | 0.367 |
| Blood | 3 | 597/1146 | 1.24 (1.05-1.47) | 0.480 | 0.013 | 1.06 (0.85-1.33) | 0.691 | 0.578 | 2.12 (1.36-3.30) | 0.263 | 0.001 | 1.17 (0.95-1.44) | 0.722 | 0.142 | 2.08 (1.34-3.22) | 0.225 | 0.001 |
| Digestive | 6 | 4462/4930 | 0.95 (0.83-1.08) | 0.003 | 0.443 | 0.98 (0.85-1.13) | 0.026 | 0.773 | 0.84 (0.71-1.01) | 0.108 | 0.058 | 0.96 (0.82-1.12) | 0.006 | 0.598 | 0.85 (0.72-1.01) | 0.241 | 0.067 |
| Breast | 2 | 1090/1063 | 0.79 (0.68-0.91) | 0.364 | 0.001 | 0.86 (0.72-1.03) | 0.475 | 0.093 | 0.42 (0.27-0.66) | 0.810 | <0.001 | 0.80 (0.68-0.95) | 0.380 | 0.012 | 0.45 (0.29-0.71) | <0.001 | 0.909 |
| Others | 1 | 560/500 | 0.79 (0.64-0.97) | - | 0.027 | 0.78 (0.60-1.01) | - | 0.060 | 0.67 (0.38-1.17) | - | 0.158 | 0.76 (0.59-0.98) | - | 0.033 | 0.73 (0.42-1.27) | - | 0.261 |
| Ethnicity | | | | | | | | | | | | | | | |
| East Asian | 17 | 10212/11725 | 0.92 (0.85-1.00) | <0.001 | 0.044 | 0.89 (0.82-0.97) | 0.012 | 0.006 | 0.90 (0.72-1.11) | <0.001 | 0.315 | 0.89 (0.81-0.98) | 0.001 | 0.013 | 0.93 (0.76-1.14) | <0.001 | 0.492 |
| West Asian | 1 | 235/254 | 0.38 (0.29-0.50) | - | <0.001 | 0.47 (0.27-0.82) | - | 0.008 | 0.21 (0.12-0.36) | - | <0.001 | 0.30 (0.18-0.49) | - | <0.001 | 0.35 (0.24-0.50) | - | <0.001 |
| Source | | | | | | | | | | | | | | | |
| HB | 12 | 6722/8310 | 0.94 (0.85-1.03) | <0.001 | 0.194 | 0.89 (0.81-0.98) | 0.041 | 0.022 | 0.97 (0.74-1.27) | <0.001 | 0.803 | 0.90 (0.81-1.00) | 0.006 | 0.056 | 1.00 (0.78-1.30) | <0.001 | 0.976 |
| PB | 6 | 3725/3669 | 0.78 (0.60-1.00) | <0.001 | 0.048 | 0.84 (0.69-1.02) | 0.007 | 0.077 | 0.61 (0.37-1.02) | <0.001 | 0.061 | 0.77 (0.60-0.99) | <0.001 | 0.043 | 0.68 (0.45-1.02) | 0.001 | 0.065 |
| Method | | | | | | | | | | | | | | | |
| TaqMan | 14 | 9472/10550 | 0.90 (0.83-0.98) | <0.001 | 0.011 | 0.88 (0.81-0.97) | 0.005 | 0.008 | 0.84 (0.70-1.01) | 0.011 | 0.066 | 0.88 (0.80-0.97) | 0.001 | 0.008 | 0.88 (0.74-1.04) | 0.036 | 0.134 |
| PCR-RFLP | 3 | 415/846 | 0.89 (0.34-2.30) | <0.001 | 0.807 | 0.77 (0.44-1.34) | 0.047 | 0.360 | 1.25 (1.16-9.53) | <0.001 | 0.829 | 0.75 (0.29-1.96) | <0.001 | 0.555 | 1.47 (0.26-8.18) | <0.001 | 0.659 |
| Sequenom | 1 | 560/583 | 0.84 (0.69-1.03) | - | 0.089 | 0.91 (0.72-1.17) | - | 0.467 | 0.45 (0.23-0.91) | - | 0.027 | 0.86 (0.68-1.09) | - | 0.225 | 0.47 (0.23-0.94) | - | 0.033 |
| rs1883965 G/A | | | | | | | | | | | | | | | |
| Total | 4 | 4300/4420 | 1.12 (1.00-1.24) | 0.203 | 0.045 | 1.15 (1.02-1.29) | 0.484 | 0.019 | 0.91 (0.54-1.54) | 0.114 | 0.733 | 1.14 (1.02-1.27) | 0.328 | 0.026 | 0.89 (0.53-1.51) | 0.120 | 0.673 |
| Cancer type | | | | | | | | | | | | | | | |
| Urinary | 1 | 1004/1051 | 1.06 (0.85-1.32) | - | 0.621 | 1.05 (0.82-1.34) | - | 0.700 | 1.21 (0.44-3.34) | - | 0.718 | 1.06 (0.83-1.34) | - | 0.655 | 1.20 (0.43-3.32) | - | 0.728 |
Table 2: Continued.

| Variables | N   | Case/control | OR (95% CI) | \( P_{\text{heter}} \) | P | OR (95% CI) | \( P_{\text{heter}} \) | P | OR (95% CI) | \( P_{\text{heter}} \) | P | OR (95% CI) | \( P_{\text{heter}} \) | P |
|-----------|-----|--------------|-------------|-----------------|---|-------------|-----------------|---|-------------|-----------------|---|-------------|-----------------|---|
| Digestive | 3   | 3296/3369    | 1.13 (1.09-1.28) | 0.115 | 0.044 | 1.18 (1.03-1.34) | 0.415 | 0.014 | 0.82 (0.44-1.53) | 0.056 | 0.538 | 1.16 (1.02-1.32) | 0.228 | 0.022 | 0.80 (0.43-1.49) | 0.061 | 0.483 |
| Source    |     |              |             |                 |    |             |                 |    |             |                 |    |             |                 |    |             |                 |
| HB        | 1   | 1048/1052    | 0.94 (0.75-1.17) | - | 0.563 | 1.03 (0.81-1.31) | - | 0.792 | 0.20 (0.04-0.92) | - | 0.038 | 0.98 (0.78-1.24) | - | 0.889 | 0.20 (0.04-0.91) | - | 0.038 |
| PB        | 3   | 3252/3368    | 1.18 (1.04-1.33) | 0.484 | 0.009 | 1.19 (1.04-1.36) | 0.489 | 0.011 | 1.28 (0.71-2.32) | 0.626 | 0.416 | 1.19 (1.05-1.36) | 0.479 | 0.009 | 1.25 (0.69-2.26) | 0.627 | 0.467 |

HB: hospital based; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; PB: population based. *Number of case-control studies. \( P_{\text{heter}} \): value of heterogeneity test.
subpopulations (https://www.ncbi.nlm.nih.gov/snp). The expression of mTOR in human tissues was evaluated by another database (http://genomics-cancer-pku.cn/). Gene expression profiles of mTOR across various types of cancers and paired normal tissues were also assessed. We also employed online databases to detect the expression of mTOR in three main urinary system cancer, gene-gene connection, and overall survival time (http://ualcan.path.uab.edu/analysis.html; http://gepia.cancer-pku.cn/index.html). We also used TCGA database and GEPIA databases to explore the expression of mTOR in human tissues was evaluated by another database (http://gemini.cancer-pku.cn/). Gene expression of mTOR in human tissues was evaluated by another database (http://gemini.cancer-pku.cn/).

3. Results

3.1. Characteristics of Eligible Studies. In total, 22 case-control studies comprising 14,747 cancer patients and 16,399 controls were included in the pooled analysis (Table 1). For the rs2295080 T/G variation, 18 studies with 10, 447 cancer patients and 11, 979 control subjects were analyzed. Stratified analysis by cancer type included six studies on urinary system cancer, six studies on digestive cancer, three studies on blood cancer, two studies on breast cancer, and one study on other cancer (thyroid cancer). In subgroup analysis by control source, 17 studies were hospital-based and the remaining six studies were population-based. In stratified analysis by ethnicity, 17 studies focused on East Asians and one on West Asians. In subgroup analysis by a genotype method, 14 studies utilized TaqMan assay. Three studies used polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), and one study performed Sequenom MassARRAY. For the rs1883965 G/A variation, four studies with 4,300 cancer patients and 4,420 controls were included. Three studies involved digestive cancer and one involved urinary cancer. Subgroup analysis by control source included three population-based studies and one hospital-based study. All these studies involved East Asian populations. The classic genotyping method, TaqMan assay, was adopted by all these studies. We investigated the minor allele frequencies (MAFs) of mTOR rs2295080 and rs1883965 polymorphisms in various races. The MAFs for the rs2295080 variant were as follows: Americans, 0.320; Africans, 0.284; and South Asians, 0.138 (Figure 1).

![Forest plot of ORs for the relationship between mTOR variants rs2295080 T/G (a) or rs1883965 G/A (b) and risk of cancer (heterozygous comparison, random effects) in stratification analysis by type of cancer.](image-url)
3.2. Overall and Stratified Analyses. The strength of the association between mTOR variation rs2295080 T/G or rs1883965 G/A and susceptibility of cancer is shown in Table 2. Significant correlation with the likelihood of cancer was evident for SNP rs2295080 in the pooled data. Compared with individuals with T-allele, individuals with G-allele had an 11% lower risk of cancer (95%CI = 0.80-0.98, P = 0.023, Figure 2(a)). In subgroup analysis by cancer type,
individuals carrying the G-allele had a 24% lower risk of urinary cancer, compared with those carrying the T-allele (95% CI = 0.62-0.94, P = 0.010). Similar findings were observed for the heterozygous contrast (95% CI = 0.70-0.85, P < 0.001) and dominant models (95% CI = 0.62-0.88, P = 0.001). For breast cancer, individuals with the G-allele had a 21% lower risk of cancer (95% CI = 0.68-0.91, P = 0.001). Similar results were indicated in population-based studies and using a TaqMan assay method. For the rs1883965 G/A variation, individuals carrying A-allele had a 1.24-fold higher risk of blood cancer (95% CI = 1.05-1.47, P = 0.013). Similar results were found in the homozygous contrast (95% CI = 1.36-3.30, P = 0.001) and recessive model (95% CI = 1.34-3.22, P = 0.001). In stratified analysis by ethnicity, East Asians carrying the G-allele had an 8% lower risk of cancer than those with the T-allele (95% CI = 0.85-1.00, P = 0.044). Similar findings were indicated in population-based studies and using a TaqMan assay method. For the rs1883965 G/A variation, individuals carrying A-allele had a 70% higher risk of cancer than those carrying the G-allele (95% CI = 1.05-1.47, P = 0.013). Similar results were found in the homozygous contrast (95% CI = 1.36-3.30, P = 0.001) and recessive model (95% CI = 1.34-3.22, P = 0.001). In stratified analysis by ethnicity, East Asians carrying the G-allele had an 8% lower risk of cancer than those with the T-allele (95% CI = 0.85-1.00, P = 0.044). Similar findings were indicated in population-based studies and using a TaqMan assay method.

**Figure 4:** Expression of mTOR in urinary cancer based on patients’ race. The expression of mTOR is downregulated in KIRC with Caucasian, African-American, and Asian descendants (a). Expression of mTOR is upregulated in BLCA with Caucasian and African-American descendants (b). Expression of mTOR is upregulated in Caucasian PRAD patients (c).

**Figure 5:** IHC analysis of mTOR in PRAD samples. Compared with paracancerous tissues, the expression of mTOR is upregulated in advanced cancer (P < 0.05).
a 1.12-fold higher likelihood of cancer than those carrying the G-allele (95%CI = 1.00-1.24, P = 0.045) (Figure 2(b)). In subgroup analysis by cancer type, a significant correlation with the susceptibility of digestive cancer was evident in the allelic contrast (95%CI = 1.00-1.28, P = 0.044), heterozygous (95%CI = 1.03-1.34, P = 0.014), and dominant models (95%CI = 1.02-1.32, P = 0.022). Similar results were confirmed in the population-based studies (allelic contrast, 95%CI = 1.04-1.33, P = 0.009; heterozygous comparison, 95% CI = 1.04-1.36, P = 0.011; and dominant model, 95%CI = 1.05-1.36, P = 0.009).

3.3. *In Silico and IHC Analyses of mTOR*. We used in silico tools to investigate the expression of mTOR based on sample types and the race of patients. As shown in Figure 3, the expression of mTOR was upregulated in BLCA and prostate...
cancer (PRAD) patients ($P < 0.05$, Figures 3(d) and 3(g)). However, the mTOR expression was downregulated in KIRC samples ($P < 0.05$, Figure 3(a)). For KIRC, no obvious difference in overall survival (OS) and disease-free survival (DFS) time was evident between the high and low mTOR expression groups ($P > 0.05$, Figures 3(b) and 3(c)). For BLCA, patients with high expression of mTOR appeared to have shorter DFS time than the low mTOR expression group ($P < 0.05$, Figure 3(e)). No significant difference in OS time was apparent ($P > 0.05$, Figure 3(f)). For PRAD, patients with low expression of mTOR appeared to have shorter DFS time than the high mTOR expression group ($P < 0.05$, Figure 3(h)). No significant difference in OS time was apparent ($P > 0.05$, Figure 3(i)). Regarding mTOR expression in urinary cancer based on race, downregulation was evident in Caucasian, African-American, and Asian KIRC patients ($P < 0.05$, Figure 4(a)). The expression of mTOR was upregulated in Caucasian and African-American BLCA patients ($P < 0.05$), but not in Asian patients ($P > 0.05$, Figure 4(b)). Expression of mTOR was upregulated in Caucasian PRAD patients ($P < 0.05$), but not in African-American patients ($P > 0.05$, Figure 4(c)). Expression profiles of mTOR in Asian PRAD patients could not be acquired from the online database. IHC analysis was used to investigate mTOR

**Figure 7:** Gene-gene interaction of mTOR in prostate cancer. The expression pattern of input genes in PRAD is shown in (a). Correlation analysis from TCGA samples indicates that ABHD2 ($\alpha/\beta$-hydrolase domain-containing 2 (b)), SEL1L (adaptor subunit of ERAD E3 ubiquitin ligase (c)), and C1ORF26 (SWT1 RNA endoribonuclease homolog (d)) are the most correlated genes with mTOR.
expression in 220 pathologically diagnosed PRAD participants voluntarily enrolled from our centers. The feature distribution of PRAD patients has been mentioned in our previous study [50]. Compared with paracancerous tissues, the expression of mTOR was upregulated in advanced PRAD (P < 0.05, Figure 5).

Furthermore, we adopted an online database to assess the mTOR expression in various tissues and organs of Homo sapiens. As described in Figure 6(a), mTOR was highly expressed in organs of the urinary system, especially the kidney and testis. The expression profiles of mTOR differed in different types of tumor tissues (Figure 6(b)). Compared with normal tissues, mTOR expression was downregulated in several types of carcinomas, especially KIRC, testicular tumors, and colon adenocarcinoma. The mTOR expression was especially upregulated in thymoma and lymphoma. In addition, we investigated the gene-gene correlation of mTOR. As shown in Figure 7(a), more than 24 genes interact with the mTOR gene. The most correlated genes contain the following: ABHD2 (α/β-hydrolase domain-containing 2, Figure 7(b)), SELIL (adaptor subunit of ERAD E3 ubiquitin ligase, Figure 7(c)), and C1ORF26 (SWT1 RNA endoribonuclease homolog, Figure 7(d)). STRING analysis revealed at least 30 proteins featuring protein-protein crosstalk with mTOR (Figure 8(a)). The most relevant proteins are as follows: RPS6KB1 (Ribosomal protein S6 kinase beta-1), LAMTOR5 (Regulator complex protein), RHEB (GTP-binding protein), MAPKAP1 (Target of rapamycin complex 2 subunit), LAMTOR1 (Regulator complex protein), RICTOR (Regulatory-associated protein of mTOR), EIF4EBP1 (Eukaryotic translation initiation factor 4E-binding protein 1), LAMTOR4 (Regulator complex protein 4), and LAMTOR2 (Regulator complex protein 2) (Figure 8(b)). Then Kyoto Encyclopedia of Genes and Genomes (KEGG) functional enrichment was further conducted utilizing gene set enrichment analysis (GSEA). Heat map and gene list association profiles are described in Figure 9(a). GSEA revealed that the insulin signaling pathway (Figure 9(b)), lysine degradation pathway (Figure 9(c)), and mTORsignaling pathway (Figure 9(d)) were enriched in the high mTOR expression group. GSEA also confirmed that mTOR was upregulated in PRAD (Figure 9(e)).

3.4. Sensitivity Analysis and Publication Bias. Sensitivity analysis was conducted by excluding every single study to evaluate their impact on the overall ORs. As described in Figures 10(a) and 10(b), no single study influenced the significance of ORs for the rs2295080 T/G and rs1883965 G/A mTOR variants (P < 0.05). Evaluation of publication bias through Begg’s funnel plots did not indicate significant publication bias for all five genetic models of rs2295080 (Figure 10(c), P > 0.05) or rs1883965 variants (Figure 10(d), P > 0.05).

4. Discussion

As a main controller of cell proliferation, mTOR participates in a variety of synthetic metabolic processes including lipogenesis, protein synthesis, and nucleotide biosynthesis. mTOR also inhibits catabolic processes including lysosomal biogenesis and autophagy. Inhibitors of the mTOR signaling pathway have been developed to treat some types of malignant tumors [52, 53]. Previous studies have also linked overexpression or mutation of core genes in the mTOR pathway to the occurrence, invasion, and prognosis of many carcinomas [8, 9]. Genetic variations of mTOR are widespread and could affect the function of protein by altering gene expression.
Several previous publications have assessed the association of mTOR variants rs2295080 T/G or rs1883965 G/A and susceptibility to cancer. However, the sample size of the included studies was insufficient [28, 29]. In 2017, Zhang et al. performed a meta-analysis based on 13 studies and observed a decreased risk of rs2295080 T/G variant on digestive system cancer [54]. However, their conclusion was not confirmed by another pooled analysis [10]. In total, our pooled analysis identified 22 eligible case-control studies comprising 14,747 cancer patients and 16,399 controls on the two mTOR variants. The current study sought to identify all eligible case-control studies to comprehensively assess the association between mTOR variants rs2295080 T/G or rs1883965 G/A and susceptibility to a variety of cancers. For the rs2295080 T/G variation, six studies were on urinary system cancer. For the rs1883965 G/A variation, one study was on urinary cancer. Our analysis does indicate a significant association of mTOR rs2295080 T/G and rs1883965 G/A polymorphism with the risk of cancer.

For the rs2295080 T/G SNP, a stratified analysis by cancer type revealed that the T-allele is a risk factor for urinary and breast cancer. This result is consistent with a recent published meta-analysis [10]. However, the latter study did not identify a significant association between mTOR rs2295080 T/G polymorphism and leukemia susceptibility. The possible reason may be that the sample size was relatively small. Presently, in a subgroup analysis by race, we found that the rs2295080 variation was associated with decreased cancer risk in East Asian populations. In stratification analysis by control source and genotyping method, we observed a significant association of this polymorphism in population-based studies and those using the TaqMan assay. Our results are consistent with the meta-analyses performed by Shao et al. [28]. For the rs1883965 G/A SNP, we observed that individuals carrying A-allele had a 1.12-fold higher likelihood of cancer than those carrying G-allele in the pooled data. Moreover, stratified analysis by cancer type revealed an association of the rs1883965 G/A polymorphism with increased digestive cancer susceptibility in allelic contrast, heterozygous comparison, and dominant model. This finding is consistent with those of Zhu et al. and He et al. [33, 44]. Additionally, we used in silico tools to investigate gene expression profile of mTOR in various types of cancers and normal tissues. mTOR was highly expressed in organs of the urinary system, especially in the kidney and testis tissues. The expression of mTOR was upregulated in BLCA and PRAD patients and was downregulated in KIRC samples. KIRC and BLCA patients displayed no obvious difference in OS between the high and low mTOR expression group. PRAD patients with low expression of mTOR appeared to have shorter DFS time than those with high mTOR expression. As shown in Figure 9, we used GSEA to investigate the possible signaling pathways and cancer correlated with expression of mTOR. We revealed that the mTOR signaling pathway was enriched in high mTOR expression group. Furthermore, the mTOR expression was augmented in PRAD.

Concerning mTOR expression in urinary cancer based on race, downregulated expression was evident in KIRC patients who were Caucasian, African-American, and Asian. For BLCA, the expression of mTOR was upregulated in...
Caucasians and African-Americans, but not in Asians. For PRAD, mTOR expression was upregulated in Caucasian patients, but not in African-American patients. The expression profiles of mTOR in Asian PRAD patients could not be acquired from the online database. We further used IHC analysis to investigate the mTOR expression in PRAD participants enrolled from our centers. Compared with para-cancerous tissues, the expression of mTOR was upregulated in advanced PRAD.

The present study has several limitations. First, according to the inclusion criteria, no case-control study on mTOR rs2295080 T/G or rs1883965 G/A polymorphism was included based on African or Caucasian populations. Further studies on African and Caucasian populations with various tumors are warranted. Second, the sample size of eligible studies for the rs1883965 G/A SNP was insufficient. Studies on many types of cancer including testicular cancer, thyroid carcinoma, thymoma, and lymphoma are very limited. Third, upregulated mTOR expression in advanced PRAD was based on IHS analysis. Further studies are needed to demonstrate whether the mTOR rs2295080 T/G or rs1883965 G/A mutations could affect the expression of mTOR in PRAD. The pathogenesis of cancer is complex, and it is not possible that a single mutation would have a huge impact on the progression. As described in Figure 7, more than 24 genes could participate in interactions with mTOR gene. At least 30 proteins were identified to interact with mTOR (Figure 8). Therefore, gene-gene and gene-environment interactions should be further studied to explore the correlation. Additionally, adjustment analysis of lifestyle or smoking exposure may contribute to better segregation and assessment of different groups. These analyses are warranted to be conducted by future studies.

5. Conclusion

In summary, the present study summarized all eligible data for the genetic relationship between the mTOR variants rs2295080 T/G or rs1883965 G/A and susceptibility to different cancers. Our results revealed that rs2295080 T/G polymorphism was associated with susceptibility of urinary cancer, especially in East Asians. The expression of mTOR was upregulated in BLCA and PRAD patients. GSEA revealed that the insulin signaling pathway, lysine degradation pathway, and

![Figure 10: Sensitivity analysis and Begg's funnel plot of mTOR variants. Sensitivity analysis of mTOR variant rs2295080 T/G (a) or rs1883965 G/A (b) indicated that a single study could not influence the significance of ORs. Begg's funnel plot analysis of rs2295080 T/G (c) or rs1883965 G/A (d) polymorphisms under heterozygous comparison model revealed no evidence of publication bias.](image-url)
mTOR signaling pathway were enriched in the high mTOR expression group. The expression of mTOR was positively correlated with tumor malignancy in prostate cancer subjects.

**Abbreviations**

| Abbreviation | Description |
|--------------|-------------|
| mTOR         | Mammalian target of rapamycin |
| ORs          | Odds ratios |
| GSEA         | Gene set enrichment analysis |
| IHS          | Immunohistochemical staining |
| ABHD2        | α/β-Hydrolase-domain-containing 2 |
| CI           | Confidence intervals |
| KIRC         | Kidney renal clear cell carcinoma |
| RHEB         | GTP-binding protein |
| BLCA         | Bladder cancer |
| SNP          | Single-nucleotide polymorphism |
| PRAD         | Prostate cancer |
| SEL1         | Adaptor subunit of ERAD E3 ubiquitin ligase |
| PCR-RFLP     | Polymerase chain reaction-restriction fragment length polymorphism |
| C10RF26      | RNA endoribonuclease homolog |
| DFS          | Disease-free survival |
| HWE          | Hardy-Weinberg equilibrium |
| RPS6KB1      | Ribosomal protein S6 kinase beta-1 |
| OS           | Overall survival |

**Data Availability**

All the data generated in the present research are available by the corresponding authors after reasonable request.

**Ethical Approval**

The above study was based on the Declaration of Helsinki and was approved by the Ethics Committee of the Affiliated Changzhou No. 2 People’s Hospital of Nanjing Medical University.

**Conflicts of Interest**

The authors declare no conflict of interests.

**Authors’ Contributions**

L.Z. (Lifeng Zhang), Y.Z., and Y.M. conceived the study design. Z.M., H.P., and B.T. searched the database and screened the articles. Y.S., Z.Z., and Z.L. performed the IHS experiments. H.W. and L.Z. (Lifeng Zhang) carried out the statistical analyses. H.P. and Y.Z. wrote the manuscript. C.L. and L.Z. (Lifeng Zhang) revised the manuscript. L.Z. (Li Zuo) and L.Z. (Lifeng Zhang) provided financial assistance. All authors have approved the final manuscript.

**Acknowledgments**

This study was funded by Young Talent Development Plan of Changzhou Health Commission (No. CZQM2020065), Jiangsu Province 333 High-Level Talents Project, and Young Scientists Foundation of Changzhou No. 2 People’s Hospital (Project No. YJRC 202039). We feel appreciated for all the members who are involved the present research.

**References**

[1] R. L. Siegel, K. D. Miller, and A. Jemal, “Cancer statistics, 2019,” CA: A Cancer Journal for Clinicians, vol. 69, no. 1, pp. 7–34, 2019.
[2] W. Chen, R. Zheng, P. D. Baade et al., “Cancer statistics in China, 2015,” CA: A Cancer Journal for Clinicians, vol. 66, no. 2, pp. 115–132, 2016.
[3] R. M. Feng, Y. N. Zong, S. M. Cao, and R. H. Xu, “Current cancer situation in China: good or bad news from the 2018 Global Cancer Statistics?,” Cancer Communications, vol. 39, no. 1, p. 22, 2019.
[4] J. R. Hsiao, C. C. Chang, W. T. Lee et al., “The interplay between oral microbiome, lifestyle factors and genetic polymorphisms in the risk of oral squamous cell carcinoma,” Carcinogenesis, vol. 39, no. 6, pp. 778–787, 2018.
[5] M. Lorenzo-González, A. Fernández-Villar, and A. Ruano-Ravina, “Disentangling tobacco-related lung cancer-genome-wide interaction study of smoking behavior and non-small cell lung cancer risk,” Journal of Thoracic Disease, vol. 11, no. 1, pp. 10–13, 2019.
[6] K. H. Khan, T. A. Yap, L. Yan, and D. Cunningham, “Targeting the PI3K-AKT-mTOR signaling network in cancer,” Chinese Journal of Cancer, vol. 32, no. 5, pp. 253–265, 2013.
[7] J. A. McCubrey, L. S. Steelman, C. R. Kempf et al., “Therapeutic resistance resulting from mutations in Raf/MEK/ERK and PI3K/PTEN/Akt/mTOR signaling pathways,” Journal of Cellular Physiology, vol. 226, no. 11, pp. 2762–2781, 2011.
[8] A. M. Martelli, F. Chiarini, C. Evangelisti et al., “The phosphatidylinositol 3-kinase/AKT/mammalian target of rapamycin signaling network and the control of normal myelopoiesis,” Histology and Histopathology, vol. 25, no. 5, pp. 669–680, 2010.
[9] Y. Piao, Y. Li, Q. Xu et al., “Association of MTOR and AKT gene polymorphisms with susceptibility and survival of gastric cancer,” PloS One, vol. 10, no. 8, article e0136447, 2015.
[10] G. H. Qi, C. H. Wang, H. G. Zhang et al., “Comprehensive analysis of the effect of rs2295080 and rs2536 polymorphisms within the mTOR gene on cancer risk,” Bioscience Reports, vol. 40, no. 7, 2020.
[11] S. Zhang, W. Shi, E. S. Ramsay et al., “The transcription factor MZF1 differentially regulates murine Mtor promoter variants linked to tumor susceptibility,” The Journal of Biological Chemistry, vol. 294, no. 45, pp. 16756–16764, 2019.
[12] P. M. LoRusso, “Inhibition of the PI3K/AKT/mTOR pathway in solid tumors,” Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, vol. 34, no. 31, pp. 3803–3815, 2016.
[13] T. Tian, X. Li, and J. Zhang, “mTOR signaling in cancer and mTOR inhibitors in solid tumor targeting therapy,” International Journal of Molecular Sciences, vol. 20, no. 3, p. 755, 2019.
[14] V. S. Rodrik-Outmezguine, M. Okaniwa, Z. Yao et al., “Overcoming mTOR resistance mutations with a new-generation mTOR inhibitor,” Nature, vol. 534, no. 7606, pp. 272–276, 2016.
[15] R. A. Saxton and D. M. Sabatini, “mTOR signaling in growth, metabolism, and disease,” Cell, vol. 168, no. 6, pp. 960–976, 2017.
[16] A. R. Tee and J. Blenis, “mTOR, translational control and human disease,” Seminars in Cell & Developmental Biology, vol. 16, no. 1, pp. 29–37, 2005.

[17] D. Liko and M. N. Hall, “mTOR in health and in sickness,” Journal of Molecular Medicine, vol. 93, no. 10, pp. 1061–1073, 2015.

[18] S. M. Ayuk and H. Abrahamse, “mTOR signaling pathway in cancer targets photodynamic therapy in vitro,” Cell, vol. 8, no. 5, p. 431, 2019.

[19] A. Alayev and M. K. Holz, “mTOR signaling for biological control and cancer,” Journal of Cellular Physiology, vol. 228, no. 8, pp. 1658–1664, 2013.

[20] M. Cargnello, J. Tcherkezian, and P. P. Roux, “The expanding role of mTOR in cancer cell growth and proliferation,” Mutagenesis, vol. 30, no. 2, pp. 169–176, 2015.

[21] C. Ciccarese, M. Brunelli, R. Montironi et al., “The prospect of precision therapy for renal cell carcinoma,” Cancer Treatment Reviews, vol. 49, pp. 37–44, 2016.

[22] P. Korkolopoulou, G. Levidou, E. A. Trigka et al., “A comprehensive immunohistochemical and molecular approach to the PI3K/AKT/mTOR (phosphoinositide 3-kinase/β-akt murine thymoma viral oncogene/mammalian target of rapamycin) pathway in bladder urothelial carcinoma,” BJU International, vol. 110, no. 11c, pp. E1237–E1248, 2012.

[23] F. Sahin, R. Kannangai, O. Adegbola, J. Wang, G. Su, and K. E. Tasioudi, S. Sakellariou, G. Levidou et al., “Single amino-acid changes that confer constitutive activation of mTOR, translational control and cancer,” Experimental and Molecular Medicine, vol. 16, no. 1, pp. 29–37, 2015.

[24] J. Zhu, M. Wang, M. Zhu et al., “Association of PI3KR1 and mTOR Polymorphisms with Esophageal Squamous Cell Carcinoma Risk and Gene-Environment Interactions in Eastern Chinese Populations,” Scientific Reports, vol. 5, no. 1, 2015.

[25] M. Xu, Y. Gao, T. Yu et al., “Functional promoter rs2295080 T>G variant in MTOR gene is associated with risk of colorectal cancer in a Chinese population,” Biomedicine & Pharmacotherapy, vol. 70, pp. 28–32, 2015.

[26] J. Zhu, M. Wang, M. Zhu et al., “Association of PI3K/AKT/mTOR Polymorphisms in esophageal squamous cell carcinoma and risk of esophageal squamous cell carcinoma in a Chinese population,” PLoS One, vol. 8, no. 3, article e58180, 2013.

[27] A. Narayanankutty, “PI3K/Akt/mTOR pathway as a therapeutic target for colorectal cancer: a review of preclinical and clinical evidence,” Current Drug Targets, vol. 20, no. 12, pp. 1217–1226, 2019.

[28] A. J. Brookes, “The essence of SNPs,” Gene, vol. 234, no. 2, pp. 177–186, 1999.

[29] T. Sato, A. Nakashima, L. Guo, K. Coffman, and F. Tamanori, “Single amino-acid changes that confer constitutive activation of mTOR are discovered in human cancer,” Oncogene, vol. 29, no. 18, pp. 2746–2752, 2010.

[30] J. Shao, Y. Li, P. Zhao et al., “Association of mTOR polymorphisms with cancer risk and clinical outcomes: a meta-analysis,” PLoS One, vol. 9, no. 5, article e97085, 2014.

[31] J. Zining, X. Lu, H. Caiyun, and Y. Yuan, “Genetic polymorphisms of mTOR and cancer risk: a systematic review and updated meta-analysis,” Oncotarget, vol. 7, no. 5, pp. 57464–57480, 2016.

[32] Q. Chen, X. Deng, X. Hu et al., “Breast cancer risk-associated SNPs in the mTOR promoter region and breast cancer risk in a sample of Iranian population,” EXCLI Journal, vol. 17, pp. 3–13, 2018.

[33] L. Qi, K. Sun, Y. Zhuang, J. Yang, and J. Chen, “Study on the association between PI3K/AKT/mTOR signaling pathway gene polymorphism and susceptibility to gastric cancer,” Journal of BUON: official journal of the Balkan Union of Oncology, vol. 22, pp. 1488–1493, 2017.

[34] J. Z. L. Zhang, S. Li, J. Liu, Q. Cao, C. Qin, and C. Yin, “Polymorphism of the mTOR gene is associated with risk of gastric cancer in a Chinese population,” PLoS One, vol. 8, no. 3, article e60080, 2013.

[35] Q. Li, C. Gu, Y. Zhu et al., “Polymorphisms in the mTOR gene and risk of sporadic prostate cancer in an eastern Chinese population,” PLoS One, vol. 8, no. 8, article e71968, 2013.

[36] L. Huang, J. Huang, P. Wu et al., “Association of genetic variations in mTOR with risk of childhood acute lymphoblastic leukemia in a Chinese population,” Leukemia & Lymphoma, vol. 53, no. 5, pp. 947–951, 2012.

[37] J. Chen, P. Shao, Q. Cao et al., “Genetic variations in a PTEN/AKT/mTOR axis and prostate cancer risk in a Chinese population,” PLoS One, vol. 7, no. 7, article e40817, 2012.

[38] Q. Cao, X. Ju, P. Li et al., “A functional variant in the MTOR promoter modulates its expression and is associated with renal cell cancer risk,” PLoS One, vol. 7, no. 11, article e50302, 2012.

[39] J. He, M. Y. Wang, L. X. Qiu et al., “Genetic variations of mTORC1 genes and risk of gastric cancer in an Eastern Chinese population,” Molecular Carcinogenesis, vol. 52, Supplement 1, pp. 70–79, 2013.

[40] H. C. Y. Zhao, T. Dang, and Y. B. Jia, “An association study between SNP rs2295080 in mTOR gene and non-cardiagastriac cancer,” Journal of Clinical Medicine Research, vol. 2, pp. 6–8, 2017.

[41] J. S. L. Wen, “Association of genetic polymorphisms in the mTOR promoter region with thyroid cancer morbidity in Han population,” Guizhou Medical University, vol. 42, pp. 1149–1154, 2017.
renal cell carcinoma,” *Journal of Modern Urology*, vol. 20, pp. 340–346, 2015.

[48] P. Y. X. Zhao, H. Xiong, J. Li, H. Li, and X. He, “Analysis Of Polymorphism Of Mtor Gene In Children With Leukemia,” *Journal of Clinical Pediatrics*, vol. 33, no. 5, pp. 423–425, 2015.

[49] Y. C. M. Q. Liu, D. Yang, S. K. Tan et al., “Association of mTOR polymorphisms with risk of hepatocellular carcinoma,” *Chinese Journal of Public Health*, vol. 30, pp. 593–597, 2014.

[50] L. F. Zhang, K. Xu, B. W. Tang et al., “Association between SOD2 V16A variant and urological cancer risk,” *Aging*, vol. 12, no. 1, pp. 825–843, 2020.

[51] A. Subramanian, P. Tamayo, V. K. Mootha et al., “Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 102, no. 43, pp. 15545–15550, 2005.

[52] M. Mirza-Aghazadeh-Attari, E. M. Ekrami, S. A. M. Aghdas et al., “Targeting PI3K/Akt/mTOR signaling pathway by polyphenols: implication for cancer therapy,” *Life Sciences*, vol. 255, 2020.

[53] J. C. Chamcheu, T. Roy, M. B. Uddin et al., “Role and therapeutic targeting of the PI3K/Akt/mTOR signaling pathway in skin cancer: a review of current status and future trends on natural and synthetic agents therapy,” *Cell*, vol. 8, no. 8, p. 803, 2019.

[54] Z. Zhang, Q. Chen, J. Zhang et al., “Associations of genetic polymorphisms in pTEN/AKT/mTOR signaling pathway genes with cancer risk: a meta-analysis in Asian population,” *Scientific Reports*, vol. 7, no. 1, p. 17844, 2017.