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The RTK/ERK pathway is associated with prostate cancer risk on the SNP level: A pooled analysis of 41 sets of data from case–control studies

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ABSTRACT

Prostate cancer (PCa) is a malignant disease influencing numerous men worldwide every year. However, the exact pathogenesis and the genes, environment, and other factors involved have not been explained clearly. Some studies have proposed that cell signaling pathways might play a key role in the development and progression of PCa. According to our previous study, the RTK/ERK pathway containing nearly 40 genes was associated with PCa risk. On the basis of these genes, we conducted a meta-analysis with our own Chinese Consortium for Prostate Cancer Genetics (ChinaPCa) study and available studies in the databases to describe the association between the pathway and PCa on the SNP level. The results suggested that rs4764695/IGF1 (recessive model: pooled OR = 0.92, 95%CI = 0.852–0.994, $P = 0.034$; $I^2 = 0\%$, $P = 0.042$; allele analysis: pooled OR = 0.915, 95%CI = 0.874–0.958, $P = 0$; $I^2 = 0\%$, $P = 0.424$; codominant model: OR = 0.835, 95%CI = 0.762–0.916, $P = 0$; $I^2 = 0\%$, $P = 0.684$) and rs1570360/VEGF (recessive model: OR = 0.596, 95%CI = 0.421–0.843, $P = 0.003$; $I^2 = 23.9\%$, $P = 0.269$; codominant model: OR = 0.576, 95%CI = 0.404–0.820, $P = 0.002$; $I^2 = 49.1\%$, $P = 0.140$) were significantly associated with PCa. In subgroup analysis, the relationship was also found in Caucasians for IGF1 (dominant model: OR = 0.834, 95%CI = 0.769–0.904, $P = 0$; allele analysis: OR = 0.908, 95%CI = 0.863–0.955, $P = 0$; AA vs CC: OR = 0.829, 95%CI = 0.750–0.916, $P = 0$; AC vs CC: OR = 0.837, 95%CI = 0.768–0.912, $P = 0$). In addition, in Asians (allele analysis: OR = 0.21, 95%CI = 0.168–0.262, $P = 0$) and Caucasians (recessive model: OR = 0.453, 95%CI: 0.240–0.855, $P = 0.015$; codominant model: OR = 0.464, 95%CI = 0.240–0.898, $P = 0.023$) for VEGF, the association was significant. The results indicated that rs4764695/IGF1 and rs1570360/VEGF might play a key role in the development and progression of PCa. On the SNP level, we suggest that the study gives us a new view of gene-pathway analysis and targeted therapy for PCa.

Abbreviations: PCa, prostate cancer; ChinaPCa, Chinese Consortium for Prostate Cancer Genetics; OR, odd ratio; CI, confidence interval; RTK, receptor tyrosine kinases; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; GSEA, gene set enrichment analysis; EGFR, epidermal growth factor receptor; IGF1, insulin-like growth factor 1; EGF, epidermal growth factor; RAF1, v-raf-1 murine leukemia viral oncogene homolog 1; CNKI, China National Knowledge Infrastructure; GWAS, genome-wide association studies; HWE, Hardy–Weinberg equilibrium; BPH, benign prostatic hyperplasia; BCL2, B-cell CLL/lymphoma 2; CCND1, cyclin D1; VEGF, vascular endothelial growth factor A.

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1. Introduction

As one of the most frequent malignant diseases among men, prostate cancer (PCa) leads to enormous loss for the economy and health worldwide (Denmeade and Isaacs, 2002; Hsing et al., 2000). In 2007, an estimated 218,890 new cases and 27,050 deaths emerged in the United States (Jemal et al., 2007). Two years later, one in six men were affected, involving 192,280 new cases of PCa and 27,360 PCa-related deaths (Jemal et al., 2009). However, the real risks for PCa had not been identified, with environmental factors, genes, and their interactions under consideration. Recently, some studies have presented the close association between cell signaling pathways and PCa risk, which might provide a potential method for targeted therapy of PCa (Dilly et al., 2013; Vo et al., 2013; Z. Zhao et al., 2013).

Considering the complex pathogenesis of the cancers, the interlaced signaling pathways and cell signal transmissions inducing cell survival, development, and apoptosis (G. Zhao et al., 2013; Jung et al., 2012; Shih et al., 2012) could give us a new view of the development, progression, and prevention of cancers. Among the various pathways, the RTK/ERK pathway is reported to be significant in controlling the status of cancers with cockamamie regulatory mechanisms. As the upstream part of this pathway, receptor tyrosine kinases are cell surface receptor containing an N-terminal extracellular ligand-binding domain and a C-terminal intracellular tyrosine kinase domain with high affinity for many polypeptide growth factors, cytokines, and hormones (Pawson, 2002; Schlessinger, 2000). They could transmit signals to participate in a wide range of biological activities, such as cell proliferation, differentiation, migration, and survival, and cellular metabolism, which could result in embryonic development, growth of an organism, angiogenesis, and tumorigenesis (Kim and Bar-Sagi, 2004; McKay and Morrison, 2007). Nevertheless, it is only in combination with mitogen-activated protein kinase (MAPK), consisting of Raf, MEK, and ERK kinases, that the function of RTK can be mediated. Through the RTK/ERK pathway, cell signals are transferred from outside to inside the cell, influencing the functions of genes (Pawson, 1995), which are involved in cell proliferation, angiogenesis, and carcinogenesis.

Recently, signal pathways were said to be a promising direction in the prevention and elimination of PCa risk and PCa therapy (Al-Azayzih et al., 2012; Park et al., 2013). In addition, according to our previous meta-analysis, pathway enrichment and gene set enrichment analysis (GSEA) (Ning et al., 2011), PCa risk is associated with the RTK/ERK pathway and nearly 40 genes (EGFR, IGF1, EGF, RAF1, and so on) in this pathway show significant expression. Therefore, considering the effects of these genes in the pathway, we proposed that the RTK/ERK pathway might be a potential signaling pathway for targeted therapy in the future. Although an association between PCa risk and the genes in this pathway has

Table 1
The characteristics of the data we included in the meta-analysis. The complex population was shown in Comstock CE et al., which was looked as the independent ones for analysis.

Author	Year	Country	Race	Case	Control	SNP/gene	Methods	Case	Control	H–W
McCarron SL et al.	2002	United Kingdom	Caucasian	PCa	Health	rs1570360/VEGF	PCR	238	263	0.2462
Koike H et al.	2003	Japan	Asian	PCa	Health	rs9344/CCND1	PCR	99	115	0.0036
Lin CC et al.	2003	China	Asian	PCa	Health	rs833061/VEGF	PCR	96	119	0
Wang L et al.	2003	Japan	Asian	PCa	Health/BPH	rs9344/CCND1	PCR–RFLP	448	254	0.0645
MT Lai et al.	2005	China	Asian	PCa	Health	rs17337023/EGFR	PCR	94	118	0.504
Sfar S et al.	2006	Tunisia	Africa	PCa	Health	rs1570360/VEGF	PCR	101	100	0.6103
Sfar S et al.	2006	Tunisia	Africa	PCa	Health	rs3025039/VEGF	PCR	101	100	0.3359
Sfar S et al.	2006	Tunisia	Africa	PCa	Health	rs2010963/VEGF	PCR	101	100	0.6862
Jinchao Ge et al.	2007	China	Asian	PCa	Health	rs9344/CCND1	TaqMan	245	245	0.4558
Fukuda H et al.	2007	Japan	Asian	PCa	Health	rs833061/VEGF	PCR–RFLP	270	252	0.4038
Hirata H et al.	2008	Japan	Asian	PCa	Health	rs2279115/BCL2	PCR–RFLP	140	167	0.0323
Teixeira AL et al.	2008	Portugal	Caucasian	PCa	Health	rs4444903/EGF	PCR–RFLP	123	152	0.0002
Onen IH et al.	2008	Turkey	Caucasian	PCa	Health	rs833061/VEGF	PCR	133	157	0.0006
Jacobs EJ et al.	2008	Mix	Caucasian	PCa	Health	rs1570360/VEGF	TaqMan	1158	1172	0
Kibel AS et al.	2008	European	Caucasian	PCa	Health	rs9344/CCND1	Pyrosequencing	184	216	0.2844
Sarma AV et al.	2008	African-American	Caucasian	PCa	Health	rs5742657/IGF1	PCR	130	330	0.1958
Sarma AV et al.	2008	African-American	Caucasian	PCa	Health	rs7965399/IGF1	PCR	130	330	0.7963
Comstock CE et al.	2010	African American	Caucasian	PCa	Health	rs9344/CCND1	Immunohistochemistry	675	647	0.0797
Comstock CE et al.	2010	Latino	Caucasian	PCa	Health	rs9344/CCND1	Immunohistochemistry	643	646	0.9539
Comstock CE et al.	2010	Japan	Asian	PCa	Health	rs9344/CCND1	Immunohistochemistry	457	467	0.6911
Comstock CE et al.	2010	Native Hawaiian	Caucasian	PCa	Health	rs9344/CCND1	Immunohistochemistry	71	68	0.8138
Comstock CE et al.	2010	European American	Caucasian	PCa	Health	rs9344/CCND1	Immunohistochemistry	456	449	0.8002
Comstock CE et al.	2010	Australian	Caucasian	PCa	Health	rs9344/CCND1	Immunohistochemistry	829	739	0.3486
Schumacher FR et al.	2010	Denmark, Great Britain, Germany, Greece, Italy, Netherlands, Spain, and Sweden	Caucasian	PCa	Health	rs4764695/IGF1	TaqMan	5827	6376	0.7033
VanCleave TT et al.	2010	America	Mix	PCa	Health	rs3025040/VEGF	PCR	191	658	0.7931
VanCleave TT et al.	2010	America	Mix	PCa	Health	rs699947/VEGF	PCR	190	635	0.1159
Mandal RK et al.	2012	India	Asian	PCa	Health	rs9344/CCND1	RFLP	192	224	0.0129
ChinaPCa	2012	China	Asian	PCa	Health	rs4444903/EGF	BeadChips	1416	1006	0.0224
ChinaPCa	2012	China	Asian	PCa	Health	rs17337023/EGFR	BeadChips	1381	986	0.0012
ChinaPCa	2012	China	Asian	PCa	Health	rs2279115/BCL2	BeadChips	1402	1005	0.5937
ChinaPCa	2012	China	Asian	PCa	Health	rs9344/CCND1	BeadChips	127	105	0.8056
ChinaPCa	2012	China	Asian	PCa	Health	rs4764695/IGF1	BeadChips	1417	1008	0.6371
ChinaPCa	2012	China	Asian	PCa	Health	rs5742657/IGF1	BeadChips	1362	976	0.0586
ChinaPCa	2012	China	Asian	PCa	Health	rs7965399/IGF1	BeadChips	1409	1004	0.561
ChinaPCa	2012	China	Asian	PCa	Health	rs833061/VEGF	BeadChips	1493	999	0.5942
ChinaPCa	2012	China	Asian	PCa	Health	rs1570360/VEGF	BeadChips	1402	1007	0.9854
ChinaPCa	2012	China	Asian	PCa	Health	rs3025039/VEGF	BeadChips	1417	1007	0.0885
ChinaPCa	2012	China	Asian	PCa	Health	rs2010963/VEGF	BeadChips	1331	952	0.4457
ChinaPCa	2012	China	Asian	PCa	Health	rs3025040/VEGF	BeadChips	1390	996	0.5198
ChinaPCa	2012	China	Asian	PCa	Health	rs699947/VEGF	BeadChips	1403	954	0.62
Meyer A et al.	2013	Germany	Caucasian	PCa	Health	rs2279115/BCL2	TaqMan	509	466	0.286