EJMO

DOI: 10.14744/ejmo.2021.46980
EJMO 2021;5(3):228–238

Research Article

A Meta-Analysis for Association of Cyclooxygenase-2 Polymorphisms with Susceptibility to Prostate Cancer

Fatemeh Asadian,[1] Hadi Maleki,[2] Sepideh Setayesh,[3] Seyed Alireza Dastgheib,[4] Mohamad Zare,[5] Saeed Kargar,[5] Seyed Hossein Shaker,[6] Mahta Mazaheri,[7,8,9] Hossein Neamatzadeh[8,9]

[1]Department of Medical Laboratory Sciences, School of Paramedical Science, Shiraz University of Medical Sciences, Shiraz, Iran
[2]Department of Urology, Alborz University of Medical Sciences, Karaj, Iran
[3]Medical Student, Shiraz University of Medical Sciences, Shiraz, Iran
[4]Department of Medical Genetics, Faculty of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[5]Department of Surgery, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[6]Department of Emergency Medicine, Iran University of Medical Sciences, Tehran, Iran
[7]Department of Medical Genetics, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[8]Mother and Newborn Health Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[9]Stem Cell Biology Research Center, Yazd Reproductive Sciences Institute, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

Abstract

A number of studies have evaluated the association of cyclooxygenase-2 (COX-2) polymorphisms with prostate cancer risk. However, the results still remain controversial. We carried out this meta-analysis to clarify the association of COX-2 polymorphisms and prostate cancer risk. An universal search in PubMed, Web of Knowledge and Google Scholar was performed to identify relevant studies up to January 2021. A total of 34 case-control studies including 11 studies with 13,248 cases and 14,768 controls were on -765G>C, 7 studies with 9,720 cases and 10,695 controls on -1195G>A, 9 studies with 11,476 cases and 11,761 controls on +202C>T, and 7 studies with 12,220 cases and 12,496 controls were on +8473T>C were selected. Pooled data showed that the COX-2 +202C>T polymorphism (T vs. C: OR= 1.305, 95% CI: 1.849-9.490; p= 0.001; TT+TC vs. CC: OR= 0.781, 95% CI: 0.669-0.913; p=0.002) was associated with risk of prostate cancer, but not the -765G>C, -1195G>A and +8473T>C polymorphisms. Stratified analyses showed that the -765G>C, -1195G>A and +202C>T polymorphisms were associated with prostate cancer risk by ethnicity. To sum up, our results indicated that the COX-2 +202C>T polymorphism was associated with risk of prostate cancer, while the -765G>C, -1195G>A and +8473T>C polymorphisms were not associated.

Keywords: Cyclooxygenase, prostate cancer, prostatic neoplasms, prostaglandin-endoperoxide synthases, polymorphism

Cite This Article: *Asadian F, Maleki H, Setayesh S, Dastgheib SA, Zare M, Kargar S, et al. A Meta-Analysis for Association of Cyclooxygenase-2 Polymorphisms with Susceptibility to Prostate Cancer. EJMO 2021;5(3):228–238.*

Prostate cancer is one of the major health concerns worldwide, particularly in more developed countries.[1,2] The highest incidence rates of prostate cancer have found among men with African-American ancestry.[3] The occurrence of prostate cancer is extremely age-dependent. However, family history and ethnicity are the only established risk factors for the prostate cancer.[4,5] Epidemiological studies have shown that the familial risk of prostate cancer increases with the number of diagnosed family members and with age at onset of the relatives.[6] Prostate cancer is

Address for correspondence: Hadi Maleki, MD. Department of Urology, Alborz University of Medical Sciences, Karaj, Iran
Phone: 00989365559119 **E-mail:** malekihadiuro@gmail.com
Submitted Date: August 03, 2021 **Accepted Date:** August 30, 2021 **Available Online Date:** September 24, 2021

suggested to arise from a combination of genetic, lifestyle and environmental factors.[7] It is suggested that environmental factors may have a substantial role in prostate cancer incidence. However, genetic factors are major components of prostate cancer development.[8,9] The contribution of genetic factors to the risk of prostate cancer is evident, but genetic susceptibility of aggressive prostate cancer is unclear.[8,10] To date, several genetic variants identified as the highest prostate cancer risk. Most of them, identified via genome-wide association study (GWAS), are located in introns or gene deserts. Furthermore, several known prostate cancer risk regions have shown functional associations with genes.[11–13]

The cyclooxygenases (COXs), also known as prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase), are a family of myeloperoxidases, which catalyzes the first two steps in the biosynthesis of prostaglandins (PGs) and located at the luminal side of the endoplasmic reticulum (ER) and nuclear membrane.[14–17] As a pro-inflammatory enzyme, cyclooxygenase-2 (COX-2) enhanced tremendously in response to pro-inflammatory and mitogenic stimuli resulting in redundant synthesis of prostaglandins from arachidonic acid. A body of evidence indicates a role for COX-2 in tumorigenesis due to its influence on cell proliferation, cell apoptosis, angiogenesis and immune response through various mechanisms [18]. Human COX-2 gene mapped in 1q25.2-q25.3, encompass 10 exons and is 8.3 kb in size.[19,20] Functional genetic variations in COX-2 may alter the expression and activity of COX-2 enzyme, and therefore affect the individual's susceptibility to prostate cancer several potentially functional variants related to prostate cancer risk have been identified in the Cox-2 gene, of which three functional SNPs, -765G>C (rs20417), -1195G>A (rs689466) in the promoter region, and the +8473 C>T (rs5275) and +202C>T in the 3'UTR region, have been widely studied.[20] The first study for -765G>C, -1195G>A, +202C>T, and +8473T>C polymorphism evaluating those polymorphisms influence on the risk to develop prostate cancer was published in 2004,[21] 2007[22] and 2006,[23] respectively. However, the primary studies based on a limited sample size were largely unsuccessful in detecting robust associations. Thus, we performed a systematic review and meta-analysis to clarify the association between COX-2 gene polymorphisms and prostate cancer risk.

Materials and Methods

Search Strategy

A systematic literature search was performed using the US National Library of Medicine's PubMed, Scopus, EMBASE, Web of Knowledge, Cochrane Library, Google Scholar, Scientific Information Database (SID), WanFang, VIP, Chinese Biomedical Database (CBD), Scientific Electronic Library Online (SciELO) and China National Knowledge Infrastructure (CNKI) database to identify relevant articles evaluated the association of COX-2 polymorphisms with risk of prostate cancer up to 1 January, 2021. Key search terms used were as follows: (''Prostate Cancer'' OR ''Prostatic Neoplasia'' OR '' Prostatic Adenocarcinoma'') AND (''Cyclooxygenase-2'' OR "COX-2" OR ''Prostaglandin-Endoperoxide Synthase 2'' OR "PTGS2") AND (''rs20417'' OR ''-765G>C'' OR ''rs689466'' OR ''-1195G>A'' OR ''rs2745557'' OR ''+202C>T'' OR ''rs5275'' OR ''+8473T>C'') AND (''Gene'' OR ''Genotype'' OR ''Allele'' OR ''Polymorphism'' OR '' Single nucleotide polymorphisms'' OR ''SNP'' OR ''Variation'' OR ''Mutation''). In addition, the reference lists of each eligible studies, previous meta-analyses and review articles were manually searched to find other relevant publications. Articles were limited to English and Chinese language papers.

Inclusion Criteria

Studies were selected if meet the following criteria: 1) full-text articles; 2) case-control or cohort studies; 3) studies the focused on the association of COX-2 polymorphisms and risk of prostate cancer; (4) Sufficient data for estimating an odds ratio (OR) or relative risk with 95% confidence interval (CI). Accordingly, the major exclusion criteria were: 1) Studies did not evaluate the association of COX-2 polymorphisms and risk of prostate cancer; 2) studies focusing on animals or in vitro; 3) Studies that did not provide usable or sufficient data for pooling; 4) case only studies or no controls; 5) linkage studies and family based studies (twins and sibling); 6) case reports, abstracts, comments, conference abstracts, editorials, reviews, meta-analysis; and 7) duplicated studies or data. When duplicated studies were published by the same author obtained from the same patient sample, only the one with the largest sample size was included in this meta-analysis.

Data Extraction

In a standardized form, two authors independently and carefully extracted the necessary data from all eligible studies. In cases where both authors did not reached a consensus, third author was consulted to make a final decision. The following data were extracted: first author, year of publication, country origin, ethnicity, total number of cases and controls, the frequencies of genotypes, genotyping technique, minor allele frequency (MAF) and Hardy-Weinberg equilibrium (HWE) in controls. In case of disagreement, consensus was obtained by discussion, or a third author would assess these articles.

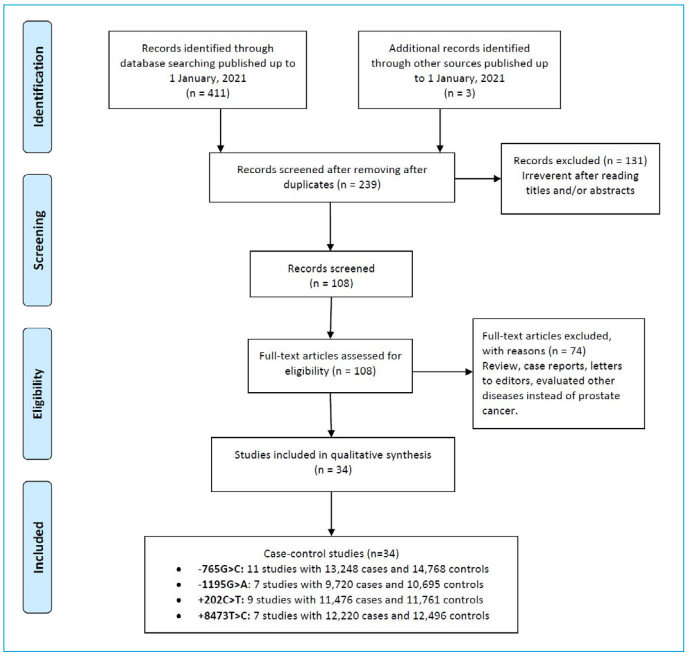

Figure 1. Flowchart of literature search and selection process.

Statistical Analysis

Crude odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated to evaluate the strength of association between COX-2 polymorphisms and prostate cancer risk in whole population. The pooled ORs were estimated under all five genetic comparison models, i.e., allele (A vs. B), homozygote (AA vs. BB), heterozygote (BA vs. BB), dominant (AA+BA vs. BB), and recessive (AA vs. BA+BB). Between-study heterogeneity was estimated using a Cochran-based Q statistical test, with P-values less than 0.1 indicated the absence of indicated heterogeneity among studies. Moreover, a quantitative measure of between-study heterogeneity was tested using the I2 statistic (range of 0 to 100%), in which the heterogeneity was considered low, moderate, and high based on I2 values of 25%, 50%, and 75%, respectively. If the between-study heterogeneity was statistically significant the random effects model (DerSimonian and Laird method) was used; otherwise, the fixed effects model (Mantel Haenszel method) was applied. For each study, the Hardy–Weinberg equilibrium (HWE) in controls was estimated using the chi-square goodness-of-fit test. Sensitivity analyses were performed to assess the stability of the results by sequential removing of each study.[24,25] To evaluate the possible publication bias, Egger's test (linear regression method) and Begg's test (rank correlation method) were used, and P values of <0.05 were considered representative of significant statistical publication bias. If publication bias existed, the Duval and Tweedie non-parametric "trim-and-fill" method was used to adjust the results accordingly. All statistical analyses were performed using the Comprehensive Meta-Analysis (CMA) software version 2.0 (Biostat, USA). Two-sided probability (P) values of <0.05 were considered statistically significant.

Results

Study Characteristics

Based on the search criteria, initially 413 studies were identified with duplicate studies removed resulting in 239 studies remaining. Among them, 131 publications were excluded based on titles and abstracts. Following the inclusion exclusion criteria 74 studies were excluded (Fig. 1). Finally, a total of 34 case-control studies (in 18 publications) were included in the present meta-analysis.[21,22,33–39,23,26–32] The characteristics of the included studies were summarized in Table 1. Of them, eleven case-control studies with 13.248 cases and 14.768 controls were on -765G>C (rs20417), seven studies with 9.720 cases and 10.695 controls on -1195G>A (rs689466) polymorphism, nine studies with 11.476 cases and 11.761 controls on +202C>T rs2745557 polymorphism, and seven studies with 12.220 cases and 12,496 controls were on +8473T>C (rs5275) polymorphism. For -765G>C polymorphism, six studies were from Caucasians, two studies were from Asians and three studies were from Africans. For -1195G>A polymorphism, three studies were from Caucasians, three studies were from Asians and one study was from Africans. For +202C>T polymorphism, six studies were from Caucasians, one study was from Asians and two studies were from Africans. For +8473T>C polymorphism, five studies were from Caucasians, one study was from Asians and Africans. The countries of these studies included USA, UK, Italy, Denmark, Sweden, China, Japan, India, Nigeria, and Egypt. Of them, three studies did not satisfy the HWE for -765G>C (rs20417) polymorphism, one for -1195G>A (rs689466) polymorphism, and one for +8473T>C (rs5275) polymorphism.

Quantitative Data Synthesis

-765G>C (rs20417) Polymorphism

Table 2 listed the main results of the meta-analysis of -765G>C (rs20417) polymorphism and prostate cancer risk. When all the eligible studies were pooled into the meta-analysis of -765G>C (rs20417) polymorphism, no significant association was observed under all five genetic models (Fig. 2a, b). In the stratified analyses based on ethnicity, there was a significant association between -765G>C (rs20417) polymorphism and increased risk of prostate cancer among Caucasians under the recessive model (CC vs. CG+GG: OR= 1.520, 95% CI: 1.172-1.973; p= 0.002), but not among Africans.

Table 1. Details of included studies in the met-analysis

First Author	Country (Ethnicity)	Total NO.	Cases					Controls					MAFs	HWE
			Genotypes			Allele		Genotypes			Allele			
-765G>C			**GG**	**CG**	**CC**	**G**	**C**	**GG**	**CG**	**CC**	**G**	**C**		
Panguluri 2004	Nigeria (African)	87/90	86	1	0	173	1	88	2	0	178	2	0.011	0.915
Panguluri 2004	Nigeria (African)	260/256	202	52	6	456	64	205	42	9	452	60	0.117	≤0.001
Cheng 2007	USA (Caucasian)	416/417	294	115	7	703	129	293	113	11	699	135	0.161	0.978
Cheng 2007	USA (African)	89/88	38	42	9	118	60	38	38	12	114	62	0.352	0.614
Murad 2009	UK (Caucasian)	1592/3028	1104	451	37	2659	525	2137	819	72	5093	963	0.159	0.534
Balistreri 2010	Italy (Caucasian)	50/125	31	15	4	77	23	65	46	14	176	74	0.296	0.190
Wu 2011	China (Asian)	218/436	198	20	0	416	20	365	71	0	801	71	0.081	0.064
Catsburg 2012	USA (Caucasian)	1431/756	892	469	70	2369	493	481	237	38	1199	313	0.207	0.214
Joshi 2012	USA (Caucasian)	935/756	595	304	36	1494	376	481	237	38	1199	313	0.207	0.214
Dossus 2009	USA (Caucasian)	7975/8566	5561	2155	259	13277	2673	5999	2299	268	14297	2835	0.165	0.008
Mandal 2011	India (Asian)	195/250	132	55	8	319	71	180	57	13	417	83	0.166	0.005
-1195G>A			**GG**	**AG**	**AA**	**G**	**A**	**GG**	**AG**	**AA**	**G**	**A**		
Cheng 2007	USA (Caucasian)	416/417	270	134	13	672	160	280	122	15	682	152	0.182	0.705
Cheng 2007	USA (African)	89/88	67	20	2	158	20	77	12	0	164	12	0.067	0.495
Dossus 2009	USA (Caucasian)	7975/8566	5089	2493	403	12655	3295	5530	2652	398	13690	3442	0.200	≤0.001
Wu 2011	China (Asian)	218/436	61	100	57	222	214	122	210	104	454	418	0.479	0.464
Kopp 2013	Denmark (Caucasian)	334/334	210	111	13	531	137	210	112	12	632	136	0.203	0.533
Sugie 2014	Japan (Asian)	134/86	52	61	21	165	103	19	47	20	85	87	0.505	0.387
Cui 2015	China (Asian)	543/753	203	269	71	675	411	217	378	158	812	694	0.460	0.779
+202C>T			**CC**	**CT**	**TT**	**C**	**T**	**CC**	**CT**	**TT**	**C**	**T**		
Shahedi 2006	Sweden (Caucasian)	1355/765	945	376	34	2266	2165	545	205	15	1295	235	0.153	0.396
Cheng 2007	USA (Caucasian)	417/417	295	107	15	695	570	262	142	13	666	168	0.201	0.232
Cheng 2007	USA (African)	89/89	69	19	1	157	122	56	30	3	140	36	0.202	0.673
Dossus 2009	USA (Caucasian)	7941/8527	5614	2098	229	10541	9928	5954	2338	235	14093	2961	0.173	0.029
Fradet 2009	USA (Caucasian)	466/478	337	129 (CT+TT)	-	-	301	177 (CT+TT)	-	-	NA	NA		
Salinas 2010	USA (Caucasian)	335/396	225	110 (CT+TT)	-	-	251	145 (CT+TT)	-	-	NA	NA		
Wu 2011	China (Asian)	218/436	165	49	4	353	83	320	107	9	746	126	0.145	0.936
Amirian 2011	USA (Caucasian)	535/533	372	163 (CT+TT)	-	-	353	180 (CT+TT)	-	-	-	NA		
Fawzy 2016	Egypt (African)	120/120	20	76	15	124	116	6	30	84	40	184	0.8235	0.141
+8473T>C			**TT**	**CT**	**CC**	**T**	**C**	**TT**	**CT**	**CC**	**T**	**C**		
Shahedi 2006	Sweden (Caucasian)	1355/765	571	618	158	1770	940	306	363	88	985	545	0.356	0.207
Cheng 2007	USA (Caucasian)	416/417	183	199	34	565	267	196	177	44	569	265	0.317	0.667
Cheng 2007	USA (African)	89/88	12	39	38	63	115	11	49	29	70	106	0.601	0.162
Danforth 2008	USA (Caucasian)	1143/1383	488	515	143	1491	795	641	605	137	1887	879	0.317	0.740
Danforth2008	USA (Caucasian)	1137/1135	517	507	113	1541	733	501	517	117	1519	751	0.330	0.332
Dossus 2009	USA (Caucasian)	7975/8566	3419	3465	1006	10413	5537	3664	3709	1092	11168	5964	0.348	0.001
Mandal 2011	India (Asian)	195/250	71	86	38	228	162	105	113	32	323	177	0.354	0.852

Table 2. The meta-analysis of COX-2 gene polymorphism and prostate cancer risk

Subgroup	Genetic model	Type of model	Heterogeneity			Odds ratio		Publication Bias		
			I^2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
-765G>C	C vs. G	Fixed	40.10	0.081	0.988	0.944-1.033	-0.539	0.590	0.119	0.118
	CC vs. GG	Fixed	0.00	0.871	0.970	0.847-1.111	-0.433	0.665	0.047	0.001
	CG vs. GG	Fixed	6.743	0.379	1.024	0.970-1.081	0.864	0.387	0.436	0.623
	CC+CG vs. GG	Fixed	0.00	0.445	1.018	0.967-1.073	0.683	0.495	0.161	0.314
	CC vs. CG+GG	Fixed	0.00	0.856	0.961	0.840-1.099	-0.580	0.562	0.076	≤0.001
By ethnicity										
Caucasians	C vs. G	Fixed	52.04	0.064	0.990	0.945-1.037	-0.416	0.677	0.259	0.181
	CC vs. GG	Fixed	0.00	0.703	0.985	0.857-1.133	-0.208	0.835	0.135	0.020
	CG vs. GG	Fixed	0.00	0.869	1.024	0.969-1.083	0.848	0.396	0.259	0.677
	CC+CG vs. GG	Fixed	0.00	0.822	1.020	0.967-1.075	0.714	0.475	0.259	0.366
	CC vs. CG+GG	Fixed	0.00	0.839	1.462	1.272-1.681	5.346	≤0.001	0.132	0.099
Africans	C vs. G	Fixed	0.00	0.792	0.994	0.749-1.320	-0.038	0.969	0.335	0.296
	CC vs. GG	Fixed	0.00	0.888	0.715	0.350-1.461	-0.920	0.358	NA	NA
	CG vs. GG	Fixed	0.00	0.750	1.180	0.822-1.695	0.896	0.370	0.296	0.099
	CC+CG vs. GG	Fixed	0.00	0.781	1.090	0.775-1.534	0.496	0.620	0.296	0.129
	CC vs. CG+GG	Fixed	26.77	0.243	1.332	0.655-2.710	0.791	0.429	NA	NA
-1195G>A	A vs. G	Random	78.30	≤0.001	0.936	0.791-1.109	-0.761	0.447	1.000	0.532
	AA vs. GG	Random	77.10	≤0.001	0.817	0.549-1.216	-0.996	0.319	1.000	0.531
	AG vs. GG	Random	56.04	0.034	0.961	0.813-1.137	-0.462	0.644	0.763	0.618
	AA+AG vs. GG	Random	72.80	0.001	0.936	0.763-1.147	-0.642	0.518	1.000	0.542
	AA vs. AG+GG	Random	67.25	0.005	0.883	0.651-1.197	-0.803	0.422	0.763	0.664
By ethnicity										
Caucasians	A vs. G	Fixed	0.00	0.953	1.036	0.984-1.091	1.350	0.177	1.000	0.928
	AA vs. GG	Fixed	0.00	0.877	1.092	0.950-1.255	1.244	0.214	1.000	0.455
	AG vs. GG	Fixed	0.00	0.782	1.028	0.964-1.095	9.845	0.398	1.000	0.438
	AA+AG vs. GG	Fixed	0.00	0.849	1.034	0.973-1.099	1.068	0.285	1.000	0.735
	AA vs. AG+GG	Fixed	0.00	0.837	1.084	0.944-1.243	1.146	0.252	1.000	0.501
Asians	A vs. G	Random	77.98	0.011	0.784	0.581-1.058	-1.591	0.112	1.000	0.996
	AA vs. GG	Random	79.60	0.007	0.609	0.324-1.147	-1.534	0.125	1.000	0.976
	AG vs. GG	Fixed	39.43	0.192	0.772	0.633-0.941	-2.558	0.011	1.000	0.687
	AA+AG vs. GG	Fixed	64.91	0.058	0.724	0.600-0.874	-3.372	0.001	1.000	0.852
	AA vs. AG+GG	Random	75.48	0.017	0.743	0.452-1.219	-1.176	0.239	1.000	0.937

-1195G>A (rs689466) Polymorphism

Table 2 also listed the main results of the meta-analysis of -1195G>A (rs689466) polymorphism and prostate cancer risk. When all the eligible studies were pooled into the meta-analysis of -1195G>A (rs689466) polymorphism, no significant association was observed in any genetic model (Fig. 3a, b). Subgroup analysis by ethnicity showed that there was a significant association between -1195G>A (rs689466) polymorphism and increased risk of prostate cancer among Asians under the heterozygote model (AG vs. GG: OR= 0.772, 95% CI: 0.633-0.941; p= 0.011) and dominant model (AA+AG vs. GG: OR= 0.724, 95% CI: 0.600-0.874; p= 0.001), but not among Caucasians.

+202C>T (rs2745557) Polymorphism

The main results of +202C>T (rs2745557) polymorphism meta-analysis were listed in Table 3. Overall, there was a significant association between +202C>T (rs2745557) polymorphism and prostate cancer under the allele model (T vs. C: OR= 1.305, 95% CI: 1.849-9.490; p= 0.001, Fig. 4a) and the dominant model (TT+TC vs. CC: OR= 0.781, 95% CI: 0.669-0.913; p= 0.002, Fig. 4b). Subgroup analysis by ethnicity showed that there was a significant association between +202C>T (rs2745557) polymorphism and increased risk of prostate cancer among Caucasian (T vs. C: OR= 11.404, 95% CI: 5.921-21.965; p≤0.001 and TT+TC vs. CC: OR= 0.847, 95% CI: 0.800-0.897; p=0.005)

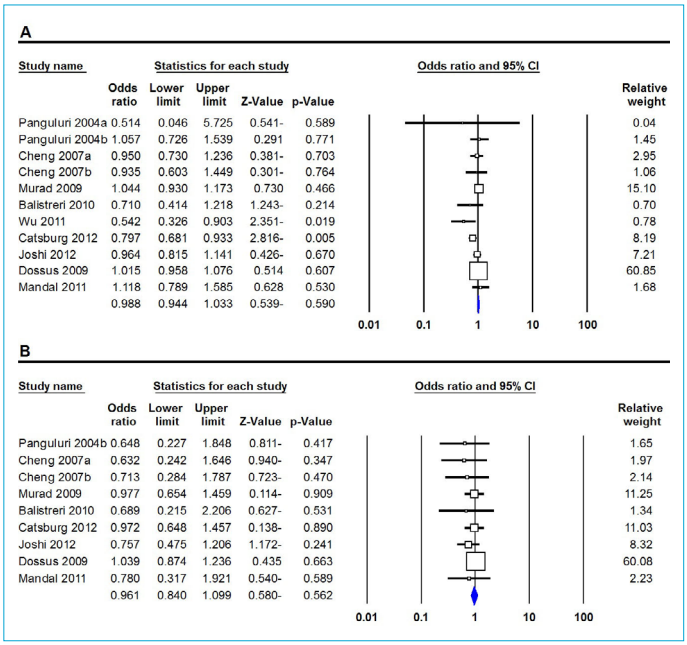

Figure 2. Forest plot for association of the COX-2 -765G>C polymorphism with prostate cancer risk in overall population. **(a)** allele model (C vs. G); **(b)** recessive model (CC vs. CG+GG).

and Africans (TT vs. CC: OR= 0.071, 95% CI: 0.027-0.188; p≤0.001; TT+TC vs. CC: OR= 0.340, 95% CI: 0.199-0.581; p≤0.001 and TT vs. TC+CC: OR= 0.070, 95% CI: 0.037-0.132, p≤0.001).

+8473T>C (rs5275) Polymorphism

Table 3 also listed the main results of the meta-analysis of +8473T>C (rs5275) polymorphism and prostate cancer risk. When all the eligible studies were pooled into the meta-analysis of +8473T>C (rs5275) polymorphism, no significant association was observed in any genetic model (Fig. 5a, b). Moreover, in the stratified analyses based on ethnicity, there was not still significant association between +8473T>C (rs5275) polymorphism and risk of prostate cancer (Table 3).

Test of Heterogeneity

As shown in Table 2 and 3, there was a significant heterogeneity existed under most genetic models for COX-2 -1195G>A and +202C>T polymorphisms. we carried out subgroup analyses by ethnicity to find the potential source of heterogeneity. Results showed that Caucasians and Africans descent subjects have not overall effect on the heterogeneity for the COX-2 -1195G>A and +202C>T polymorphisms, respectively. Moreover, in the current meta-analysis the I2 statistics is very high in almost subgroup analysis which show that most of the variability between studies is due to heterogeneity rather than chance.

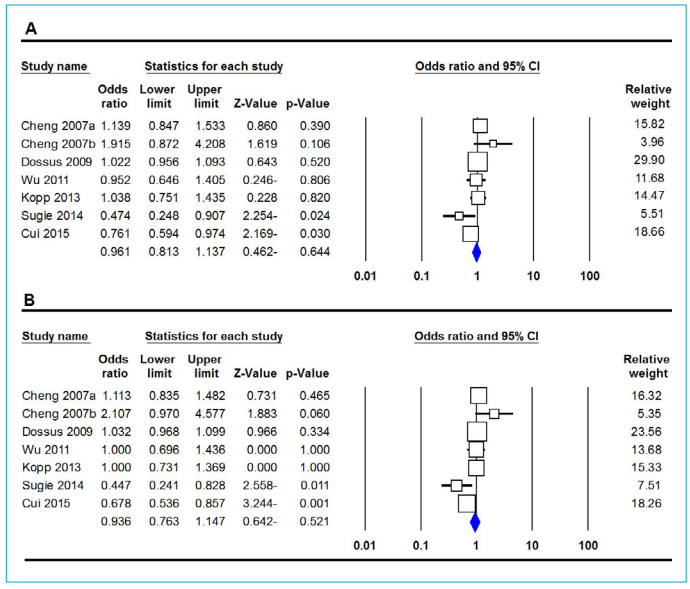

Figure 3. Forest plot for association of the COX-2 -1195G>A polymorphism with prostate cancer risk in overall population. A: heterozygote model (AG vs. GG); B: dominant model (AA+AG vs. GG).

Sensitivity Analyses and Publication Bias

We performed the sensitivity analyses to assess the robustness of the results by removing each study in turn and all the results were not essentially altered, suggesting that the results of the present meta-analysis were statistically stable. Publication bias of the eligible literature was evaluated by funnel plots and the shapes of funnel plots for literature about association between four polymorphisms and risk of prostate cancer. The shapes of the funnel plots for three studied polymorphisms showed no obvious asymmetry, except for -765G>C (rs20417) polymorphism under two genetic models, i.e., homozygote model (PBeggs =0.047; PEggers=0.001) and recessive (PBeggs =0.076; PEggers≤0.001). Therefore, the Duval and Tweedie non-parametric "trim-and-fill" method was used to adjust for publication bias. Meta-analyses with and without using the "trim-and-fill" method did not draw different conclusions (Fig. 6a, b).

Discussion

The etiology of prostate cancer is complicated, and several risk factors are involved in the development of this disease.[40,41] In addition to environmental and lifestyle risk factors, genetic causes, such as single gene mutations, also play essential roles in prostate cancer. the current meta-analysis was performed to provide a clear understanding the association of COX-2 polymorphisms with risk of prostate cancer.[42] COXs are necessary for the metabolic conversion of arachidonic acid to prostaglandins, including PGE2, a major mediator of inflammation and angiogenesis.[16,43] COX-2 is an inducible prostaglandin H synthase involved in the pro-

Table 3. The meta-analysis of COX-2 gene polymorphism and prostate cancer risk.

Subgroup	Genetic model	Type of model	Heterogeneity			Odds ratio		Publication Bias		
			I^2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
+202C>T	T vs. C	Random	99.08	≤0.001	4.189	1.849-9.490	3.434	0.001	0.259	0.471
	TT vs. CC	Random	83.87	≤0.001	0.597	0.282-1.261	-1.352	0.176	0.060	0.304
	TC vs. CC	Fixed	48.37	0.085	0.883	0.754-1.033	-1.552	0.121	0.452	0.222
	TT+TC vs. CC	Random	68.73	0.001	0.781	0.669-0.913	-3.103	0.002	0.047	0.176
	TT vs. TC+CC	Random	98.57	≤0.001	0.881	0.109-7.114	-0.118	0.906	0.707	0.047
By ethnicity										
Caucasians	T vs. C	Random	98.44	≤0.001	11.404	5.921-21.965	7.278	≤0.001	1.000	0.525
	TT vs. CC	Fixed	0.00	0.772	1.052	0.885-1.251	0.578	0.563	1.000	0.572
	TC vs. CC	Random	68.26	0.043	0.912	0.759-1.097	-0.976	0.329	1.000	0.712
	TT+TC vs. CC	Fixed	54.42	0.052	0.847	0.800-0.897	-5.696	0.005	0.707	0.763
	TT vs. TC+CC	Random	97.90	≤0.001	2.857	0.400-20.391	1.047	0.295	1.000	0.072
Africans	T vs. C	Random	99.13	≤0.001	1.559	0.055-43.96	0.261	0.794	NA	NA
	TT vs. CC	Fixed	36.66	0.209	0.071	0.027-0.188	-5.356	≤0.001	NA	NA
	TC vs. CC	Fixed	0.00	0.527	0.580	0.331-1.016	-1.905	0.057	NA	NA
	TT+TC vs. CC	Fixed	71.99	0.059	0.340	0.199-0.581	-3.947	≤0.001	NA	NA
	TT vs. TC+CC	Fixed	46.56	0.171	0.070	0.037-0.132	-8.149	≤0.001	NA	NA
+8473T>C	C vs. T	Fixed	38.68	0.134	1.011	0.974-1.049	0.555	0.578	0.229	0.242
	CC vs. TT	Fixed	41.51	0.114	1.021	0.942-1.108	0.511	0.609	0.548	0.412
	CT vs. TT	Fixed	0.00	0.509	1.008	0.955-1.063	0.281	0.779	0.763	0.814
	CC+CT vs. TT	Fixed	13.63	0.326	1.014	0.964-1.066	0.533	0.594	1.000	0.567
	CC vs. CT+TT	Fixed	44.80	0.092	1.072	0.928-1.238	0.948	0.343	0.548	0.304
By ethnicity										
Caucasian	C vs. T	Fixed	31.31	0.213	1.004	0.967-1.043	0.231	0.817	1.000	0.752
	CC vs. TT	Fixed	37.82	0.169	1.008	0.929-1.095	0.194	0.846	0.806	0.887
	CT vs. TT	Fixed	11.54	0.340	1.007	0.954-1.063	0.249	0.803	0.806	0.671
	CC+CT vs. TT	Fixed	26.68	0.244	1.011	0.960-1.063	0.405	0.685	0.806	0.671
	CC vs. CT+TT	Fixed	31.07	0.214	1.007	0.932-1.088	0.181	0.856	0.806	0.950

duction of prostaglandins (PG).[44,45] An increasing number of studies have demonstrated that COX-2/PGE signaling pathway is involved in the progression of benign prostatic hyperplasia (BPH).[46,47]

The current meta-analysis is the largest and most comprehensive assessment of the association of the COX-2 polymorphisms with risk prostate cancer. The current meta-analysis was included 11 studies relating to the -765G>C (rs20417) polymorphism (13,248 cases and 14,768 controls), 7 studies relating to the -1195G>A (rs689466) polymorphism (9,720 cases and 10,695 controls), 9 studies relating to the +202C>T (rs2745557) polymorphism (11,476 cases and 11,761 controls), and 7 studies relating to the +8473T>C (rs5275) polymorphism (12,220 cases and 12,496 controls). The pooled data revealed that the COX-2 +202C>T (rs2745557) polymorphism was significantly associated with an increased risk of prostate cancer in overall population. However, the -765G>C (rs20417),-1195G>A (rs689466) and +8473T>C (rs5275) polymorphisms were not statistically significantly associated with susceptibility to prostate cancer. Similarly, Feng et al., in a meta-analysis based on nine studies with 5952 cases and 5078 controls showed that the COX2 -765G>C polymorphism was not associated with prostate cancer risk.[48] Yang et al., in a meta-analysis of 5 case control studies revealed that the +8473T>C polymorphism may have little association with risk of prostate cancer in Caucasians, but not in other ethnicities.[49]

These results were not in agreement with previous meta-analyses. In 2012, Zhang et al. aggregated eight articles to evaluate the association between the COX-2 +202C>T (rs2745557) polymorphism and prostate cancer risk. Their results showed that the this polymorphism was not associated with prostate cancer in overall population.[50] This could be partially attributable to the relatively small sample size. Interestingly, compared with the Zhang et al. study, only

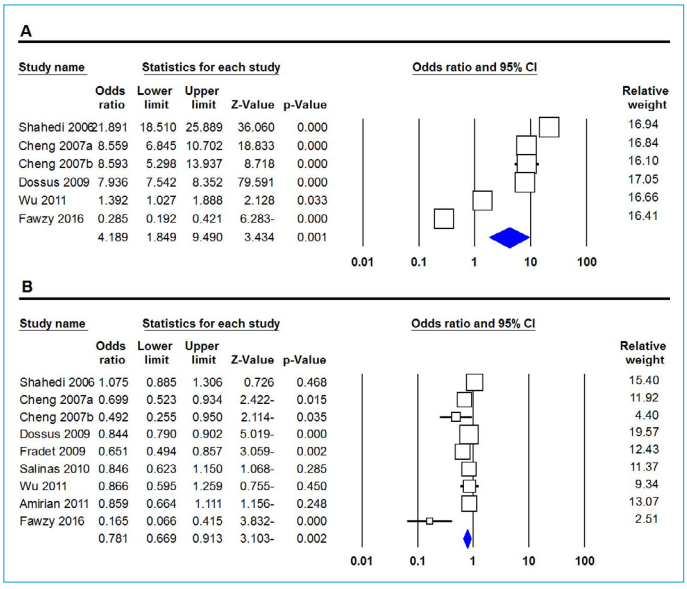

Figure 4. Forest plot for association of the COX-2 +202C>T polymorphism with prostate cancer risk in overall population. **(a)** allele model (T vs. C); **(b)**: dominant model (TT vs. TC+CC).

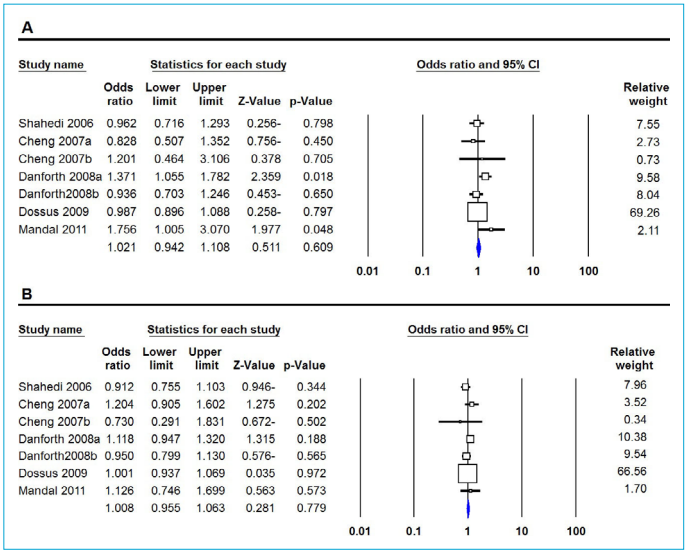

Figure 5. Forest plot for association of the COX-2 +8473T>C polymorphism with prostate cancer risk in overall population. **(a)** homozygote model (CC vs. TT); **(b)** heterozygote model (CT vs. TT).

one additional study with 120 cases and 120 controls was included in the current meta-analysis, from which different evidence could be provided on the association between COX-2 +202C>T (rs2745557) poly-morphism and risk of prostate cancer. Therefore, considering the limited studies included in the meta-analysis, this may increase the risk of false negative findings, any conclusions at overall population level should be interpreted with caution. Thus, in spite of the negative findings between this study and previous meta-analyses, it does not mean that the these polymorphisms are not biologically functional, and it is possible

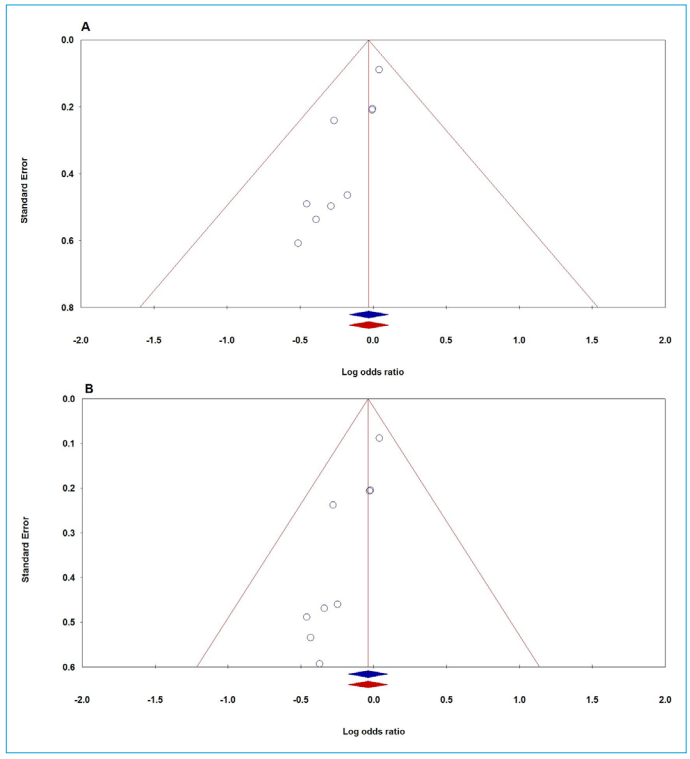

Figure 6. The funnel plots of publication bias for association of the COX-2 -765G>C polymorphism with prostate cancer risk in overall population. **(a)** homozygote model (CC vs. GG) and **(b)** recessive model (CC vs. CG+GG).

that the relative risk attributable to a single allele is small. The main possible reason for this discrepancy might be the enlarged sample size in the current meta-analysis with previous meta-analyses.

The presence of heterogeneity and publication bias might distort the conclusion of the meta-analyses and result in an erroneous and potentially misleading conclusion.[51,52] The heterogeneity might be explained by sampling errors and the small number of samples in some studies or chance or real differences in populations or in interactions with other risk factors.[53] To explore the sources of heterogeneity for COX-2 -1195G>A and +202C>T polymorphisms, a subgroup analysis by ethnicity was carried out. The results showed that the heterogeneity was significantly reduced or disappeared in Caucasians and Africans, respectively; which indicated that ethnicity could partly explain the source of heterogeneity. The studies for the Asians and Caucasians for -1195G>A and +202C>T polymorphisms yielded different results, with high heterogeneity, revealing the necessity for further study. Moreover, we performed sensitivity and stratified analyses to identify the sources of heterogeneity. However, the results did not essentially changed, suggesting that our pooled data of were stable.

When interpreting the results of the this meta-analysis, there are still several limitations that should be taken with cause. First, the number of included studies was relatively small in African and mixed populations. Therefore, the association of COX-2 polymorphisms with risk of prostate cancer in African and mixed remained unclear. Second, the studies included in this meta-analysis were published in English. Unpublished studies or studies published in non-English studies were not included in our study, which the publication bias was unavoidable. Third, substantial heterogeneity was observed for COX-2 -1195G>A and +202C>T polymorphisms. However, subgroup analysis and sensitivity analyses revealed that this heterogeneity could not be fully explained by the results. Fourth, its OR values were unadjusted data, due to the lack of data of age, eating habits, smoking, chemical exposure, alcoholic consumption, family history, obesity and other environmental exposure factors. Finally, we reported only crude estimates of genetic association and did not measure gene-gene or gene-environment interactions due to lack of original data in primary studies.

In summary, this meta-analysis results indicated that the COX-2 +202 C>T (rs2745557) polymorphism was associated with an increased risk of prostate cancer in overall population. However, the COX-2 -765G>C, -1195G>A and +8473T>C polymorphisms were not associated. However, large sample size, well-designed, and population-based studies should be performed to verify the association COX-2 polymorphisms with prostate cancer risk.

Disclosures

Ethics Committee Approval: This article does not contain any studies with human participants or animals performed by any of the authors.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – F.A., H.M., S.A.D.; Design – M.Z., S.K., H.N.; Supervision – S.A.D., F.A., M.M.; Materials – H.N., S.H.S., M.M.; Data collection &/or processing – H.N.; Analysis and/or interpretation – S.A.D., H.N.; Literature search – S.A.D., H.N.; Writing – All authors; Critical review – S.A.D., F.A., M.M.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87–108. [CrossRef]
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66:7–30. [CrossRef]
3. Odedina FT, Akinremi TO, Chinegwundoh F, Roberts R, Yu D, Reams RR, et al. Prostate cancer disparities in Black men of African descent: a comparative literature review of prostate cancer burden among Black men in the United States, Caribbean, United Kingdom, and West Africa. Infect Agent Cancer 2009;4(Suppl 1):S2. [CrossRef]
4. Perez-Cornago A, Key TJ, Allen NE, Fensom GK, Bradbury KE, Martin RM, et al. Prospective investigation of risk factors for prostate cancer in the UK Biobank cohort study. Br J Cancer 2017;117:1562–71. [CrossRef]
5. Bai Y, Gao YT, Deng J, Sesterhenn IA, Fraumeni JF, Hsing AW. Risk of prostate cancer and family history of cancer: a population-based study in China. Prostate Cancer Prostatic Dis 2005;8:60–5. [CrossRef]
6. Rodriguez C, Calle EE, Miracle-McMahill HL, Tatham LM, Wingo PA, Thun M, et al. Family history and risk of fatal prostate cancer. Epidemiology 1997;8:653–7. [CrossRef]
7. Gómez-Acebo I, Dierssen-Sotos T, Fernandez-Navarro P, Palazuelos C, Moreno V, Aragonés N, et al. Risk model for prostate cancer using environmental and genetic factors in the Spanish multi-case-control (MCC). Sci Rep 2017;7:8994. [CrossRef]
8. Rawla P. Epidemiology of prostate cancer. World J Oncol 2019;10:63–89. [CrossRef]
9. Shen MM, Abate-Shen C. Molecular genetics of prostate cancer: new prospects for old challenges. Genes Dev 2010;24:1967–2000. [CrossRef]
10. Balistreri CR, Candore G, Lio D, Carruba G. Prostate cancer: from the pathophysiologic implications of some genetic risk factors to translation in personalized cancer treatments. Cancer Gene Ther 2014;21:2–11. [CrossRef]
11. Ishak MB, Giri VN. A systematic review of replication studies of prostate cancer susceptibility genetic variants in high-risk men originally identified from genome-wide association studies. Cancer Epidemiol Biomarkers Prev 2011;20:1599–610.
12. Nikolić Z, Savić Pavićević D, Brajušković G. Genetic Association Studies on Prostate Cancer. In: Mohan R, ed. Prostate Cancer - Leading-edge Diagnostic Procedures and Treatments. London: InTech Open; 2016. [CrossRef]
13. Farashi S, Kryza T, Clements J, Batra J. Post-GWAS in prostate cancer: from genetic association to biological contribution. Nat Rev Cancer 2019;19:46–59. [CrossRef]
14. Sobolewski C, Cerella C, Dicato M, Ghibelli L, Diederich M. The role of cyclooxygenase-2 in cell proliferation and cell death in human malignancies. Int J Cell Biol 2010;2010:215158.
15. Chandrasekharan NV, Simmons DL. The cyclooxygenases. Genome Biol 2004;5:241. [CrossRef]
16. Rouzer CA, Marnett LJ. Cyclooxygenases: structural and functional insights. J Lipid Res 2009;50(Suppl):S29–34. [CrossRef]
17. Blobaum AL, Marnett LJ. Structural and functional basis of cyclooxygenase inhibition. J Med Chem 2007;50:1425–41.
18. Pan Y, Gao S, Qi Q, Liu L. The genetic variant of COX-2 acts as a potential risk factor of colorectal cancer: evidence from a meta-analysis based on 13461 individuals. Integr Mol Med 2015;2:440–8.

19. Zhang YC, Zhao H, Chen C, Ali MA. COX-2 gene rs689466 polymorphism is associated with increased risk of colorectal cancer among Caucasians: a meta-analysis. World J Surg Oncol 2020;18:192. [CrossRef]
20. Piranda DN, Festa-Vasconcellos JS, Amaral LM, Bergmann A, Vianna-Jorge R. Polymorphisms in regulatory regions of Cyclooxygenase-2 gene and breast cancer risk in Brazilians: A case-control study. BMC Cancer 2010;10:613. [CrossRef]
21. Panguluri RCK, Long LO, Chen W, Wang S, Coulibaly A, Ukoli F, et al. COX-2 gene promoter haplotypes and prostate cancer risk. Carcinogenesis 2004;25:961–6. [CrossRef]
22. Cheng I, Liu X, Plummer SJ, Krumroy LM, Casey G, Witte JS. COX2 genetic variation, NSAIDs, and advanced prostate cancer risk. Br J Cancer 2007;97:557–61. [CrossRef]
23. Shahedi K, Lindström S, Zheng SL, Wiklund F, Adolfsson J, Sun J, et al. Genetic variation in the COX-2 gene and the association with prostate cancer risk. Int J Cancer 2006;119:668–72.
24. Jafari-Nedooshan J, Dastgheib SA, Kargar S, Zare M, Raee-Ezzabadi A, Heiranizadeh N, et al. Association of IL-6 -174 G>C polymorphism with susceptibility to colorectal cancer and gastric cancer: a systematic review and meta-analysis. Acta Medica (Hradec Kralove) 2019;62:137–46. [CrossRef]
25. Jafari M, Jarahzadeh MH, Dastgheib SA, Seifi-Shalamzari N, Raee-Ezzabadi A, Sadeghizadeh-Yazdi J, et al. Association of PAI-1 rs1799889 Polymorphism with Susceptibility to Ischemic Stroke: a Huge Meta-Analysis based on 44 Studies. Acta Medica (Hradec Kralove) 2020;63:31–42. [CrossRef]
26. Murad A, Lewis SJ, Smith GD, Collin SM, Chen L, Hamdy FC, et al. PTGS2-899G>C and prostate cancer risk: a population-based nested case-control study (ProtecT) and a systematic review with meta-analysis. Prostate Cancer Prostatic Dis 2009;12:296-300.
27. Balistreri C, Caruso C, Carruba G, Miceli V, Campisi I, Listi F, et al. A pilot study on prostate cancer risk and pro-inflammatory genotypes: pathophysiology and therapeutic implications. Curr Pharm Des 2010;16:718–24.
28. Wu HC, Chang CH, Ke HL, Chang WS, Cheng HN, Lin HH, et al. Association of cyclooxygenase 2 polymorphic genotypes with prostate cancer in taiwan. Anticancer Res 2011;31:221–5.
29. Catsburg C, Joshi AD, Corral R, Lewinger JP, Koo J, John EM, et al. Polymorphisms in carcinogen metabolism enzymes, fish intake, and risk of prostate cancer. Carcinogenesis 2012;33:1352–9.
30. Joshi AD, Corral R, Catsburg C, Lewinger JP, Koo J, John EM, et al. Red meat and poultry, cooking practices, genetic susceptibility and risk of prostate cancer: Results from a multiethnic case-control study. Carcinogenesis 2012;33:2108–18. [CrossRef]
31. Dossus L, Kaaks R, Canzian F, Albanes D, Berndt SI, Boeing H, et al. PTGS2 and IL6 genetic variation and risk of breast and prostate cancer: Results from the Breast and Prostate Cancer Cohort Consortium (BPC3). Carcinogenesis 2010;31:455–61.
32. Mandal RK, Mittal RD. Polymorphisms in COX-2 gene influence prostate cancer susceptibility in a Northern Indian cohort. Arch Med Res 2011;42:620–6. [CrossRef]
33. Kopp TI, Friis S, Christensen J, Tjønneland A, Vogel U. Polymorphisms in genes related to inflammation, NSAID use, and the risk of prostate cancer among Danish men. Cancer Genet 2013;206:266–78. [CrossRef]
34. Sugie S, Tsukino H, Mukai S, Akioka T, Shibata N, Nagano M, et al. Cyclooxygenase 2 genotypes influence prostate cancer susceptibility in Japanese Men. Tumour Biol 2014;35:2717–21.
35. Fradet V, Cheng L, Casey G, Witte JS. Dietary omega-3 fatty acids, Cyclooxygenase-2 genetic variation, and aggressive prostate cancer risk. Clin Cancer Res 2009;15:2559–66. [CrossRef]
36. Salinas CA, Kwon EM, Fitzgerald LM, Feng Z, Nelson PS, Ostrander EA, et al. Use of aspirin and other nonsteroidal anti-inflammatory medications in relation to prostate cancer risk. Am J Epidemiol 2010;172:578–90.
37. Amirian ES, Ittmann MM, Scheurer ME. Associations between arachidonic acid metabolism gene polymorphisms and prostate cancer risk. Prostate 2011;71:1382–9.
38. Fawzy MS, Elfayoumi AR, Mohamed RH, Fatah IRA, Saadawy SF. Cyclooxygenase 2 (rs2745557) polymorphism and the susceptibility to benign prostate hyperplasia and prostate cancer in Egyptians. Biochem Genet 2016;54:326–36. [CrossRef]
39. Danforth KN, Hayes RB, Rodriguez C, Yu K, Sakoda LC, Huang WY, et al. Polymorphic variants in PTGS2 and prostate cancer risk: results from two large nested case-control studies. Carcinogenesis 2008;29:568–72.
40. Abedinzadeh M, Zare-Shehneh M, Neamatzadeh H, Abedinzadeh M, Karami H. Association between MTHFR C677T polymorphism and risk of prostate cancer: evidence from 22 studies with 10,832 cases and 11,993 controls. Asian Pac J Cancer Prev. 2015;16:4525–30. [CrossRef]
41. Abedinzadeh M, Dastgheib SA, Maleki H, Heiranizadeh N, Zare M, Jafari-Nedooshan J, et al. Association of endothelial nitric oxide synthase gene polymorphisms with susceptibility to prostate cancer: a comprehensive systematic review and meta-analysis. Urol J 2020;17:329–37.
42. Garg R, Blando JM, Perez CJ, Lal P, Feldman MD, Smyth EM, et al. COX-2 mediates pro-tumorigenic effects of PKCε in prostate cancer. Oncogene 2018;37:4735–49. [CrossRef]
43. Hanna VS, Hafez EAA. Synopsis of arachidonic acid metabolism: a review. J Adv Res 2018;11:23–32. [CrossRef]
44. Sooriakumaran P, Kaba R. The risks and benefits of cyclo-oxygenase-2 inhibitors in prostate cancer: a review. Int J Surg 2005;3:278–85. [CrossRef]
45. Wu S, Huang D, Su X, Yan H, Ma A, Li L, et al. The prostaglandin synthases, COX-2 and L-PGDS, mediate prostate hyperplasia induced by low-dose bisphenol A. Sci Rep 2020;10:13108.
46. Xie C, Sun X, Chen J, Ng CF, Lau KM, Cai Z, et al. Down-regulated CFTR during aging contributes to benign prostatic hy-

perplasia. Journal of Cellular Physiology 2015;230:1906–15. https://doi.org/10.1002/jcp.24921. [CrossRef]
47. Pang LY, Hurst EA, Argyle DJ. Cyclooxygenase-2: a role in cancer stem cell survival and repopulation of cancer cells during therapy. Stem Cells International 2016;2016:2048731.
48. Feng YQ, Li YU, Xiao WD, Wang GX, Li YO. Lack of association between the cyclooxygenase 2 -765G>C polymorphism and prostate cancer risk: a meta-analysis. Genet Mol Res 2015;14:13391–402. [CrossRef]
49. Yang X, Li B, Si T, Liu Y, Guo Z. Association between the 8473T>C polymorphism of PTGS2 and prostate cancer risk: a metaanalysis including 24,716 subjects. Onkologie 2013;36:182–6.
50. Zhang HT, Xu Y, Zhang ZH, Li L. Meta-analysis of epidemiological studies demonstrates significant association of PTGS2 polymorphism rs689470 and no significant association of rs20417 with prostate cancer. Genet Mol Res 2012;11:1642–50. [CrossRef]
51. Mashhadiabbas F, Neamatzadeh H, Nasiri R, Foroughi E, Farahnak S, Piroozmand P, et al. Association of vitamin D receptor BsmI, TaqI, FokI, and ApaI polymorphisms with susceptibility of chronic periodontitis: A systematic review and meta-analysis based on 38 case–control studies. Dent Res J (Isfahan) 2018;15:155–65. [CrossRef]
52. Gohari M, Neámatzadeh H, Jafari MA, Mazaheri M, Zare-Shehneh M, Abbasi-Shavazi E. Association between the p53 codon 72 polymorphism and primary open-angle glaucoma risk: Meta-analysis based on 11 case-control studies. Indian J Ophthalmol 2016;64:756–61. [CrossRef]
53. Aslebahar F, Neamatzadeh H, Meibodi B, Karimi-Zarchi M, Tabatabaei RS, Noori-Shadkam M, et al. Association of tumor necrosis factor-α (TNF-α) -308g>a and -238g>a polymorphisms with recurrent pregnancy loss risk: a meta-analysis. Int J Fertil Steril 2019;12:284–92.