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The 8q24 Rs10090154c>T Gene Variant and Its Association with the Risk of Prostate Cancer: A Systematic Review and Meta-analysis

8q24 Rs10090154>T Gen Varyantı ve Prostat Kanseri Riski ile İlişkisi: Sistematik Gözden Geçirme ve Meta-analiz

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ABSTRACT Objective: Genetic variation at chromosome 8q24 is considered as the potential biomarker for prostate cancer. We aimed to assess the relation between the gene variant of 8q24 rs10090154C>T and the risk of prostate cancer. **Material and Methods:** A meta-analysis was carried out in January to June 2020 by collecting relevant studies through online databases. The correlation and estimated effect between the gene variant of 8q24 rs10090154C>T and the risk of prostate cancer were analyzed using a Z test. **Results:** A total of 16 relevant studies were selected (16,842 cases and 18,258 controls). In overall, T allele and CT genotype of 8q24 rs10090154C>T gene polymorphism increased the risk of prostate cancer (OR95%CI=1.238 [1.14-1.34], p<0.001; OR95%CI=1.238 [1.14-1.35], p<0.001) while CC genotype and C allele had protective effect (OR95%CI=0.800 [0.74-0.87], p<0.001; OR95%CI=0.808 [0.75-0.88], p<0.001). Subgroup analysis of Caucasian population revealed that T allele of 8q24 rs10090154C>T was associated with increased risk of prostate cancer (OR95%CI=1.285 [1.07-1.54], p<0.001), while C allele had protective effect (OR95%CI=0.778 [0.65-0.93], p=0.007). In Asian population, CT genotype of 8q24 rs10090154C>T was correlated with increased risk of prostate cancer (OR95%CI=1.302 [1.17-1.45], p<0.001), while CC genotype had protective effect (OR95%CI=0.770 [0.64-0.92], p=0.005). **Conclusion:** Our meta-analysis confirmed that 8q24 RS10090154C>T gene polymorphism had strong association with the risk of prostate cancer.

Keywords: Prostate cancer; MYC; gene polymorphism; meta-analysis

ÖZET Amaç: Kromozom 8q24'deki genetik varyasyon prostat kanseri için potansiyel bir biyobelirteç olarak düşünülür. 8q24 rs10090154C>T gen varyantı ile prostat kanseri riski arasındaki ilişkiyi değerlendirmeyi amaçladık. **Gereç ve Yöntemler:** Çevrimiçi veri tabanlarını kullanarak Ocak-Haziran 2020 tarihleri arasındaki ilgili çalışmaları toplamak suretiyle bir meta-analiz yaptık. 8q24 rs10090154C>T gen varyantı ile prostat kanseri riski arasındaki korelasyon ve tahmini etki Z testi kullanılarak analiz edildi. **Bulgular:** Toplam 16 çalışma seçildi (16,842 olgu ve 18,258 kontrol). Toplamda, T aleli ve of 8q24 rs10090154C>T gen polimorfizminin CT genotipi prostat kanserini artırıyorken (OR, %95 GA=1.238 [1.14-1.34], p<0.001; OR %95 GA=1.238 [1.14-1.35], p<0.001) CC genotipi ve C alelinin koruyucu etkisi vardı (OR %95 GA=0.800 [0.74-0.87], p<0.001;OR %95 GA=0.808 [0.75-0.88], p<0.001). Kafkas popülasyonunun alt grup analizi, 8q24 rs10090154C>T'nin T alelinin artmış prostat kanseri riski ile ilişkili olduğunu (OR %95 GA=1.285 [1.07-1.54], p<0.001), C alelinin koruyucu etkiye sahip olduğunu ortaya çıkardı (OR %95 GA=0.778 [0.65-0.93], p=0.007). Asya popülasyonunda, 8q24 rs10090154C>T'nin CT genotipi, prostat kanseri riskinin artmasıyla korele iken (OR %95 GA=1,302 [1,17-1.45], p<0.001), CC genotipinin koruyucu etkisi vardı (OR %95 GA=0.770 [0.64] -0.92], p=0.005). **Sonuç:** Meta-analizimiz, 8q24 RS10090154C>T gen polimorfizminin prostat kanseri riski ile güçlü bir ilişkisi olduğunu doğruladı.

Anahtar Kelimeler: Prostat kanseri; MYC; gen polimorfizmi; meta-analiz

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Prostate cancer is known to be the second most prevalent malignancy in men. A total of 1,276,106 new cases were recorded in 2018, while the total number of death reached 358,989 cases.[1] In 2018, the global death rate for prostate cancer varies by region. In which reported between 3.3 and 10.7 per 100,000 population. The highest mortality rate related to prostate cancer was reported in Central America, while the lowest mortality rate was recorded in South-Central Asia. One-third of mortality occurred in Asia (33.0%), followed by Europe (29.9%). The development of prostate cancer is complex and may involve multiple etiologies with approximately 42% of cases was due to genetic factors and 58% was due to environmental or lifestyle factors.[2]

Referring to genetic factor as a predisposing factor in the development of prostate cancer, wide-scale studies in the scope of Genome-wide Association Studies (GWASs) had reported that more than 40 predisposing gene variants might be involved in the pathogenesis of prostate cancer, including single nucleotide polymorphisms (SNPs) in the 8q24 region that was considered as the most potential biomarkers for prostate cancer.[3,4] Moreover, a study also reported that genetic variation at chromosome 8q24 is linked with the risk of prostate cancer.[5] Briefly, MYC may play a pivotal role as multiple enhancers for a cancer-linked gene. Genetic variants in 8q24 loci form a long-range interaction with MYC oncogene, where even the smallest variants in enhancers may contribute to the risk of cancers, including prostate cancer.[6,7] Furthermore, several studies had identified that five 8q24 gene polymorphisms (rs6983267T>G, rs1447295C>A, rs16901979C>A, rs6983561A>C, and rs10090154C>T) might be implicated in the development of prostate cancer, and of them, the polymorphic allele of rs10090154C>T was found more prevalent in patients with prostate cancer than other SNPs.[8]

Several clinical studies had been conducted to assess the role of 8q24 rs10090154C>T gene polymorphisms in the progression of prostate cancer. However, a similar study with contradictive results was found. Moreover, previous meta-analyses on this topic had been performed, and their findings remained inconclusive with some limitations. Therefore, our study aimed to assess the implication of the 8q24 rs10090154C>T gene variant to the development of prostate cancer by considering previous studies' limitations. Our study provided a better correlation regarding the role of 8q24 rs10090154C>T gene polymorphisms in the development of prostate cancer.

MATERIAL AND METHODS

STUDY DESIGN

A meta-analysis was conducted from January to June 2020 by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.[9] The cumulative calculation to assess the association between the gene variant of 8q24 rs10090154C>T and the risk of prostate cancer determined by calculating the combined events per sample size of case and control, and the effect estimate was calculated from the combined odds ratio (OR) and 95% confidence interval (95%CI) using a Z test.

LITERATURE SEARCH STRATEGY

The keywords in our searching strategy conformed to Medical Subject Heading (MeSH); ["8q24 rs10090154C>T gene polymorphism" or "8q24 rs10090154C>T gene variant"] and ["prostate cancer" or "prostate neoplasm" or prostate carcinoma"]. The search strategy was conducted in Pubmed, ScienceDirect, and Web of Science up to 15 June 2020. To obtain additional potentially relevant articles, we also manually searched from the reference list of related studies. All included articles were in English. If we found studies with similar study data, we only selected papers with higher sample size. Moreover, to confirm that our searching strategy had an adequate standard, the searching was carried out by three independent authors (BP, MI, SS).

STUDY ELIGIBILITY

Articles included in our study should meet the following criteria; (1) designs: case-control, cross-sectional, and randomized control trial; (2) investigating the association between the gene variant of 8q24

rs10090154C>T and the risk of prostate cancer; and (3) providing the frequency of genotype for calculating OR95%CI. On the other hand, articles were excluded if they were; (1) irrelevance title or abstract; (2) editorials, commentary, and reviews; (3) unpublished papers; (4) incomplete and or unspecific data; (4) low quality; and (5) deviation from the principle of Hardy-Weinberg Equilibrium (HWE).[10]

DATA EXTRACTION

The following data from each paper were extracted using a pilot form: (1) the name of the first author; (2) publication year; (3) ethnicity; (4) presence of SNPs; (5) Newcastle-Ottawa Scale (NOS) score, and (6) the frequency of genotype of cases and controls. The calculation of allele frequency was determined using Mendel's genetic principle. The extraction process was carried out by three independent investigators (BP, MI, SS). If we found the discrepancy among investigators, we performed a consensus.

COVARIATES AND SUB-GROUP ANALYSIS

The predictor covariates in our study were alleles and genotypes of 8q24 rs10090154C>T gene polymorphism including CC vs. CT+TT; CT vs. CC+TT; TT vs. CC+CT; C vs. T; and T vs. C. While the preferred outcome was the incidence of prostate cancer. Moreover, a sub-group analysis study based on ethnicity was also performed, divided into Caucasian, Asian, and African.

QUALITY ASSESSMENT

A NOS was screened to all included papers to assess the quality of each paper. The assessment was conducted by three independent authors (BP, MI, SS). This quality assessment had three main factors; the enrollment of the patient (4 points), the group comparison (2 points), and the exposure of each group (3 points). The score ranged between zero (the worst) and 9 (the best). The score ranged between zero (the worst) and 9 (the best). A paper was considered as good in quality if the score was ≥7, moderate (score ≥5), or poor (score<5).[11] If we had a discrepancy among authors, we consulted the senior researcher (JKF).

STATISTICAL ANALYSIS

We assessed the correlation between the gene variant of 8q24 rs10090154C>T and the risk of prostate cancer by calculating the Z test, while the estimation effect was determined by calculating OR95%CI. The evaluation of potential publication bias and heterogeneity was performed before the calculation of effect estimates. An Egger test and funnel plot were employed to confirm publication bias. Potential publication bias was confirmed if the p-value was less than 0.0050. Moreover, we used a Q test to assess the heterogeneity among papers. The p-value of less than 0.100 was considered to have heterogeneity. If heterogeneity among studies was found ($p<0.100$), we applied a random effect model to assess the effect estimates. Conversely, we used a fixed-effect model if we found no heterogeneity among studies. A review manager (Revman Cochrane, London, UK) version 5.3 was used to analyze the data.

RESULTS

ELIGIBLE STUDIES

Our search strategy in the scientific database identified 135 potentially relevant papers. Six papers were excluded due to duplication, while the other 38 were excluded due to irrelevant titles and or abstracts. More after, the full-text review was done on 54 papers. Due to incomplete data, unavailable full text, and deviation from HWE; a total of 36 papers were excluded. Finally, we included a total of 16 papers in our meta-analysis.[12-27] We outline the flowchart of included papers in Figure 1, and the baseline characteristics are provided in Table 1.

DATA SYNTHESIS

Our cumulative analysis revealed that, overall, T allele and CT genotype of 8q24 rs10090154C>T gene variant increased the risk of prostate cancer (OR95%CI=1.238 [1.14-1.34], $p<0.001$; OR95%CI= 1.238 [1.14-1.35], $p<0.001$) while CC genotype and C allele had protective effect (OR95%CI=0.800 [0.74-0.87], $p<0.001$; OR95% CI=0.808 [0.75-0.88], $p<0.001$). Moreover, a sub-group analysis was also assessed, divided into Caucasian, Asian, and African. In Caucasian population, we revealed that T allele of

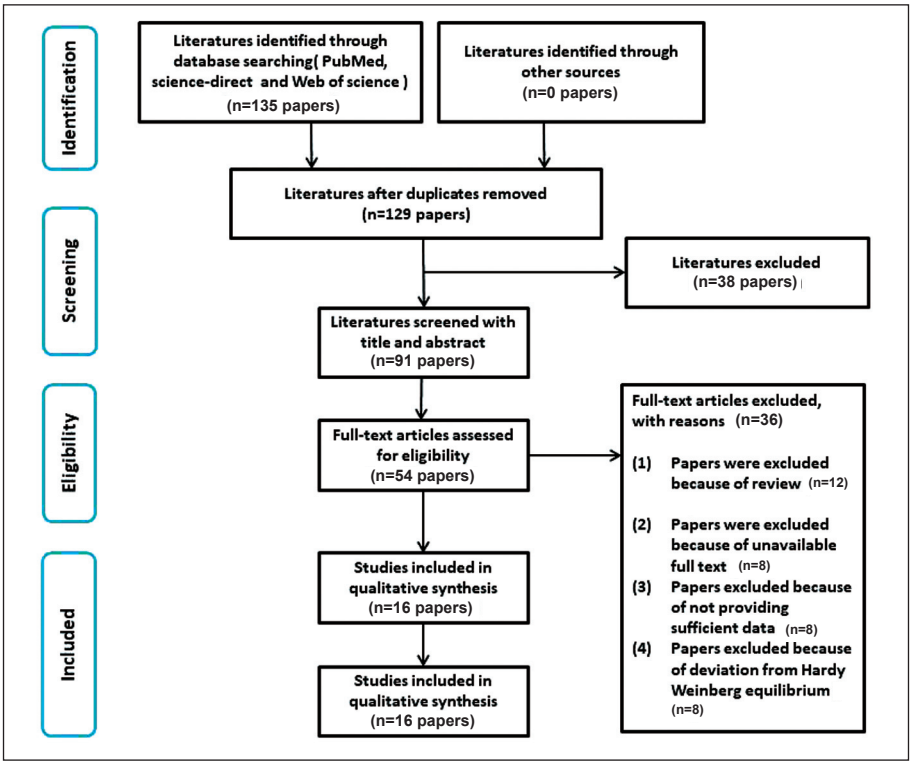

FIGURE 1: A flowchart of studies included in our meta-analysis.

TABLE 1: Baseline characteristics of studies included in our analysis.

	Case								Control									
Author and year	CC	CT	TT	N	C	T	n	HWE	CC	CT	TT	N	C	T	n	HWE	Ethnicity	NOS
Al Olama et al.[12]	5,369	417	8	5,794	11,155	433	11,588	0	5,508	321	5	5,834	11,337	331	11,668	0.02	Caucasian	9
Beebe-Dimmer et al.[13]	504	38	1	543	1,046	40	1,086	0.1	439	33	1	473	911	35	946	0.21	African	8
Benford et al.[14]	124	59	6	189	307	71	378	0.1	357	131	17	505	845	165	1,010	1.32	African	8
Chang et al.[15]	1,539	140	3	1,682	3,218	146	3,364	0.01	1,290	111	2	1,403	2,691	115	2,806	0.06	African	9
Cheng et al.[27]	52	36	1	89	140	38	178	3.72	61	24	3	88	146	30	176	0.11	African	7
Cheng et al.[16]	985	57	1	1,043	2,027	59	2,086	0.04	995	62	1	1,058	2,052	64	2,116	0.00	Caucasian	9
Liu et al.[17]	260	25	1	286	545	27	572	0.23	266	21	1	288	553	23	576	0.69	Asian	8
Murphy et al.[18]	282	26	1	309	590	28	618	0.23	427	41	1	469	895	43	938	0.00	African	8
Oskina et al.[19]	289	73	6	368	651	85	736	0.31	280	33	1	314	593	35	628	0.00	Caucasian	8
Reis et al.[26]	136	32	1	169	304	34	338	0.36	53	13	1	67	119	15	134	0.04	Caucasian	8
Saldanha et al.[20]	148	35	2	185	331	39	370	0	55	14	1	70	124	16	140	0.01	Caucasian	8
Salinas et al.[21]	968	294	26	1,288	2,230	346	2,576	0.44	1,007	230	13	1,250	2,244	256	2,500	0.00	Caucasian	9
Sun et al.[22]	205	16	0	221	426	16	442	0.31	529	31	0	560	1,089	31	1,120	0.45	Caucasian	8
Tindall et al.[23]	273	23	0	296	569	23	592	0.48	187	18	0	205	392	18	410	0.04	African	8
Wang et al.[24]	116	10	0	126	242	10	252	0.22	317	27	1	345	661	29	690	0.27	African	8
Yamada et al.[25]	280	26	1	307	586	28	614	0.23	930	75	2	1,007	1,935	79	2,014	0.14	Asian	8

HWE: Hardy Weinberg equilibrium.

8q24 rs10090154C>T was related to increased risk of prostate cancer (OR95%CI=1.285 [1.07-1.54], p<0.001), while C allele had protective effect (OR95%CI=0.778 [0.65-0.93], p=0.007). In Asian population, we found that CT genotype of 8q24 rs10090154C>T gene variant was associated with increased susceptibility to prostate cancer (OR 95%CI=1.302 [1.17-1.45], p<0.001), while CC genotype had protective effect (OR95%CI=0.770 [0.64-0.92], p=0.005). Conversely, we were unable to

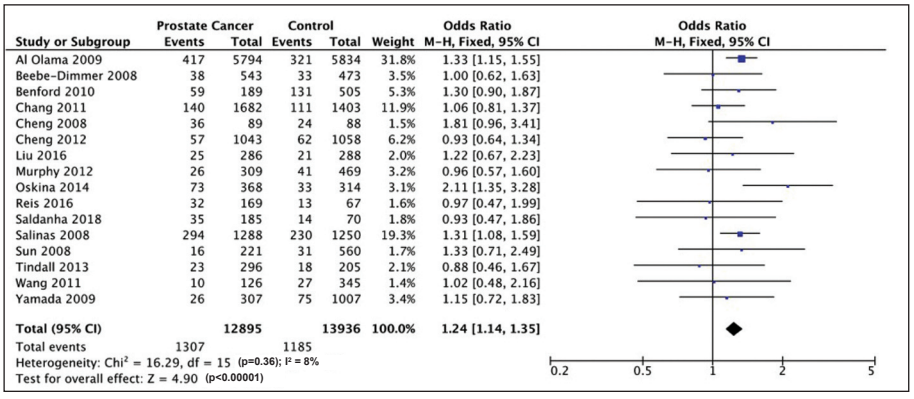

FIGURE 2: Forest plot of the association 8q24 rs10090154 gene polymorphism and the risk of prostate cancer (CT vs CC+TT).

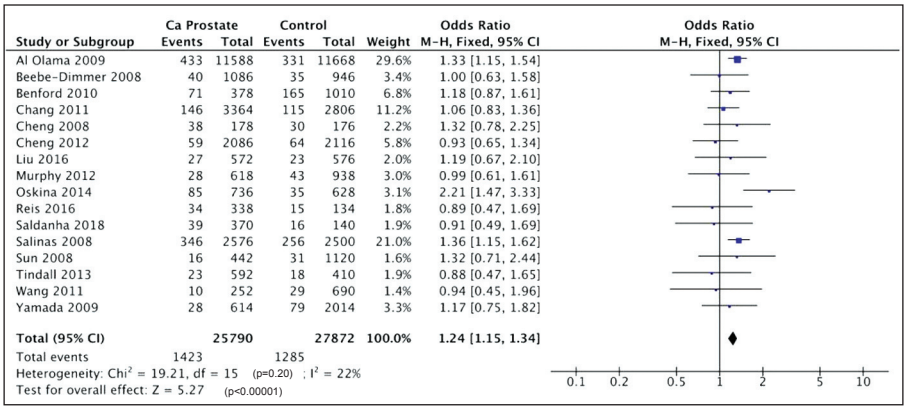

FIGURE 3: Forest plot of the association 8q24 rs10090154 gene polymorphism and the risk of prostate cancer (T vs C).

clarify the correlation between 8q24 rs10090154C>T gene variant and the risk of prostate cancer in African population. The forest plots illustrating the association between 8q24 rs10090154C>T gene polymorphism and the risk of prostate cancer are described in Figure 2 for CT vs. CC+TT and Figure 3 for T vs.C. A summary of effect estimates of the relation between the 8q24 rs10090154C>T gene variant and the risk of prostate cancer is outlined in Table 2.

HETEROGENEITY AMONG STUDIES AND PUBLICATION BIAS

Our main finding was calculated using a fixed-effect model since no evidence of heterogeneity observed in all genetic models of 8q24 rs10090154C>T gene variant. Due to no evidence of heterogeneity in African sub-groups, the impact of all genetic models on the risk of prostate cancer was also assessed using a fixed-effect model. The Caucasian sub-group was assessed with a random-effect model due to the existence of heterogeneity, C vs. T and T vs. C alleles. On the other hand, a fixed-effect model was used in all genotypes of the Caucasian subgroup due to no evidence of heterogeneity. In the Asian sub-group, evidence of heterogeneity was found on CC vs. CT+TT genotype and assessed using a random-effect model. We used a fixed-effect model in all alleles and remaining genotypes in the Asian sub-group due to no evidence of heterogeneity.

Overall, potential publication bias was found in TT vs. CC+CT genotypes. In the African sub-group, the potential publication bias was found on all genotypes and alleles. In the Caucasian sub-group, a potential publication bias was found on all genotypes. In the Asian sub-group, potential publication bias was found on C vs. T allele, T vs. C allele, and TT vs. CC+CT genotype.

TABLE 2: Summary of the association between 8q24 rs10090154C>T gene polymorphism and the risk of prostate cancer.

			Value						
Allele and genotype	**NS**	**Model**	**Case (%)**	**Control (%)**	**OR**	**95%CI**	**pH**	**pE**	**p value**
Overall analysis									
C vs. T	16	Fixed	94.48	95.39	0.808	0.75-0.88	0.205	0.092	<0.001
T vs. C	16	Fixed	5.52	4.61	1.238	1.14-1.34	0.205	0.092	<0.001
CC vs. CT+TT	16	Fixed	89.41	91.14	0.800	0.74-0.87	0.237	0.089	<0.001
CT vs CC+TT	16	Fixed	10.14	8.50	1.238	1.14-1.35	0.363	0.055	<0.001
TT vs CC+CT	14	Fixed	0.45	0.36	1.393	0.93-2.10	0.941	<0.001	0.112
Africa analysis									
C vs. T	7	Fixed	94.50	93.76	0.928	0.80-1.08	0.945	<0.001	0.337
T vs. C	7	Fixed	5.50	6.24	1.077	0.92-1.25	0.945	<0.001	0.337
CC vs. CT+TT	7	Fixed	89.36	88.24	0.912	0.78-1.07	0.800	<0.001	0.265
CT vs CC+TT	7	Fixed	10.27	11.04	1.108	0.94-1.31	0.654	<0.001	0.221
TT vs CC+CT	6	Fixed	0.37	0.72	0.909	0.45-1.85	0.958	<0.001	0.793
Caucasian analysis									
C vs. T	7	Random	95.36	96.06	0.778	0.65-0.93	0.049	0.159	0.007
T vs. C	7	Random	4.64	3.94	1.285	1.07-1.54	0.049	0.159	<0.001
CC vs. CT+TT	7	Fixed	89.41	92.36	0.847	0.59-1.21	0.922	<0.001	0.368
CT vs CC+TT	7	Fixed	10.14	7.41	1.175	0.81-1.70	0.883	<0.001	0.392
TT vs CC+CT	6	Fixed	0.45	0.23	1.332	0.22-8.20	0.794	<0.001	0.757
Asian analysis									
C vs. T	2	Fixed	94.42	95.91	0.849	0.60-1.20	0.962	<0.001	0.356
T vs. C	2	Fixed	5.58	4.09	1.178	0.83-1.67	0.962	<0.001	0.356
CC vs. CT+TT	2	Random	89.41	92.07	0.770	0.64-0.92	0.071	0.155	0.005
CT vs CC+TT	2	Fixed	10.14	7.69	1.302	1.17-1.45	0.153	0.122	<0.001
TT vs CC+CT	2	Fixed	0.45	0.24	1.760	1.04-2.96	0.722	<0.001	0.034

OR: Odd ratio; CI: Confidence interval; pH: p heterogeneity; pE: p Egger.

DISCUSSION

Our study confirmed that 8q24 rs10090154C>T gene variant was associated with the risk of prostate cancer. Of 16 papers included, we found that seven studies confirmed the association between the gene variant of 8q24 rs10090154C>T and the risk of prostate cancer. The cumulative calculation revealed that the T allele and CT genotype of 8q24 rs10090154C>T increased the risk of prostate cancer while the CC genotype and C allele decreased the risk of prostate cancer. The result of our study was consistent with previous meta-analysis studies conducted by Li et al. and Ren et al. Moreover, a GWASs study conducted by Liu et al. also found that the T allele of rs10090154C>T variant was considered as one of the risk factors of prostate cancer.[8,28,29] They revealed that the role of rs10090154C>T variant in the development of prostate cancer occurred through gene-gene interaction, and might involve other SNPs including rs10090154 and rs1447295. Furthermore, the interaction between the increased risk of prostate cancer and SNP variation of rs 1447295 was observed by several studies.[17,21] In other disease settings, some studies also found that the T allele of 8q24 rs10090154C>T was involved in the development of colorectal organ tumorigenesis.[30,31] They found that the T allele remained the important predictor in the development of tumorigenesis in colorectal cancer. Therefore, we confirmed that the 8q24 rs10090154 T allele had a strong association with the pathogenesis of prostate cancer.

In sub-group analysis; among Caucasian, Asian, and African populations; the correlation between the gene variant of 8q24 rs10090154C>T and the risk of prostate cancer was found in Caucasian and Asian populations. The correlation in the African population was failed to clarify. In the Caucasian popula-

tion, our data confirmed an increased risk of prostate cancer in the T allele, while a protective effect against prostate cancer was found in the C allele. However, in the Asian population, we observed the increased risk of prostate cancer in the CT genotype while a protective effect was observed in the CC genotype. Our current finding provided contradiction compared to the previous study.[8] They found no significant correlation between the gene variant of 8q24 rs10090154 and the risk of prostate cancer in the Caucasian and Asian populations. A study in 2016 confirmed a significant correlation between the gene variant of 8q24 rs10090154 and the risk of prostate cancer in the Asian population.[17] The contradiction between our present study and Li et al. remained inconclusive and required further investigation.[8] The reasonable explanation of the ethnicity involvement in genetic polymorphism in the context of prostate cancer remained undefined properly. However, the theory regarding the phenomenon of variations in Minor Allele Frequency (MAF) of each ethnicity might support our findings. MAF indicates the presence of risk allele, which carries the risk of disease and its variation has an inverse correlation with the effect size.[32] Subsequently, it was reported that the 8q24 rs10090154C>T MAF mutation in prostate cancer in the Caucasian population was lower than in the Asian and African populations. The effect size to govern disease development should be higher in the Caucasian and Asian populations than in the African population.[33] Therefore, the correlation between the gene variant of 8q24 rs10090154C>T and the risk of prostate cancer was found in the Caucasian and Asian populations, but not in the African population.

Theoretically, the present understanding reveals that prostate cancer has multiple risk factors including genetics and lifestyle. In the context of genetic factor, SNPs in the 8q24 region is one of the potential biomarkers for a prostate cancer diagnosis. However, the precise theory on the involvement of the 8q24 Rs10090154C>T gene polymorphism in the pathogenesis of prostate cancer has never been discussed exclusively.[2-4,30,34] The term of 8q24 is used to describe the location of a cytogenetic map of chromosome 8, arm q, band 2, and sub-band 4. Chromosome 8q24 is divided into three regions and 5 blocks. Chromosome 8q24 rs10090154 is located in region 1 Block 5.[12] The theory underlying the relation between the gene variant of rs10090154C>T and the risk of prostate cancer is not well understood. However, the speculation proposed that the correlation might occur through the MYC oncogene. The risk loci of 8q24 may create a long-range interaction with MYC oncogene and may take part in prostate cancer pathogenesis through the activity of the c-MYC gene.[7] MYC is multiple enhancers for a cancer-linked gene. Enhancers are sections of DNA (outside of the genes) that act as a modifier of the activity of the genes. MYC may activate a set of signals in a specific organ, and may interact with the same gene in different organs, but may produce different signals.[6] In the context of prostate cancer, MYC may change the activity of the PDLIM5 gene, HMGN2P46, ARHGEF17, and other genes in the prostate, causing prostate adenocarcinoma.[35] A study by Haiman et al. revealed that high cell proliferation was found in prostate cancer cells with a high C Myogen expression.[30] It was also found that amplification and overexpression of genes in 8q24 (including c-MYC) could influence the mechanism of prostate cancer. Moreover, the location between rs10090154 in region 1 of chromosome 84 and the distal location of the c-MYC gene is considered to generate gene-gene interaction that may attribute to the pathogenesis of prostate cancer.[19] However, further studies should be performed to confirm gene to gene interaction between rs10090154C>T and c-MYC in the development of prostate cancer.

The association between prostate cancer and 8q24 rs10090154C>T gene polymorphism was confirmed in our meta-analysis. This meta-analysis also confirmed the ethnicity involvement underlying the correlation between the gene variant of 8q24 rs10090154C>T and the risk of prostate cancer. A complex set of genetic methodologies using the application of HWE calculation were presented to provide accurate results. HWE is the basis of the genetics population and should be applied properly to ensure that the genetic variation in the population remains constant across the periods. Our current study might provide a better correlation quality due to the HWE principle application compared to previous relevant meta-analyses. In previous meta-analyses, we found

TABLE 3: Summary of previous meta-analysis and their limitations.

Author & year	Case setting	SNP	NS	Main Result	Limitations
Li et al.[8]	Prostate cancer	8q24	8	8q24 had association with the risk of prostate cancer	Four studies did not conform with HWE Two Studies were unavailable full text
Ren et al.[28]	Prostate cancer	8q24	11	8q24 had association with the risk of prostate cancer	Four studies did not conform with HWE

SNP: Single nucleotide polymorphism; NS: Number of studies; HWE: Hardy Weinberg equilibrium.

several included studies with HWE deviation, as summarized in Table 3.[8,28] However, our current study might be considered as "the tip of the iceberg," meaning that undefined factors that might also contribute to the development of prostate cancer were not involved in our study. Therefore, further studies in this context should be refined using more complex settings including the interaction between gene to gene, gene and other diseases, and gene to the environment. The 8q24 rs10090154C>T gene polymorphism might be considered as the clinical standard as a prostate cancer biomarker.

Several limitations were found in our current study. First, the included papers in this meta-analysis were cross-sectional. To provide better evidence, we suggested further studies with a higher study design. Second, other risk factors including family history and other genetic factors that may attribute to the pathogenesis of prostate cancer were not included in our study. Third, not all included studies elaborated on genotype and allele count. In this case, the MAF conversion was used. Fourth, the number of populations in our present study was lower compared to previous meta-analyses.

CONCLUSION

This present meta-analysis finds that 8q24 rs10090154C>T gene polymorphism had a strong association with the progression of prostate cancer. In sub-group analysis, it is also found that the relation between 8q24 rs10090154C>T gene polymorphism and the risk of prostate cancer is found in Caucasian and Asian populations. Our study provides a better correlation compared to previous meta-analyses, with a better model from the genetic perspective which emphasizes the principle of HWE. All manuscripts are checked for their compliance with the Instructions for Authors. Manuscripts not complying with the instructions will not be submitted to referees for evaluation.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Buyung Prasetya;* ***Design:*** *Buyung Prasetya, Muhammed Imawan, Jonny Karunia Fajar;* ***Control/Supervision:*** *Buyung Prasetya, Jonny Karunia Fajar, Besut Daryanto;* ***Data Collection and/or Processing:*** *Buyung Prasetya, Muhammed Imawan, Sirin Salsabila;* ***Analysis and/or Interpretation:*** *Buyung Prasetya, Muhammed Imawan, Sirin Salsabila, Jonny Karunia Fajar;* ***Literature Review:*** *Buyung Prasetya, Muhammed Imawan, Sirin Salsabila, Jonny Karunia Fajar, Besut Daryanto;* ***Writing the Article:*** *uyung Prasetya, Muhammed Imawan, Sirin Salsabila, Jonny Karunia Fajar, Besut Daryanto;* ***Critical Review:*** *Buyung Prasetya, Jonny Karunia Fajat, Besut Daryanto.*

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