DERLEME REVIEW

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The Association Between Glutathione S-Transferase P1 105IIe>Val Gene Polymorphism and the Risk of Bladder Cancer: A Meta-Analysis

Glutatyon S-Transferaz P1 105IIe>Val Gen Polimorfizmi ve Mesane Kanseri Riski: Meta-analiz

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ABSTRACT Objectives: In the last three decades, Glutathione S-Transferase P1 (GSTP1) 105IIe>Val had been extensively reported in the case of Bladder cancer (BC). However, conflicting results were observed among the studies. We aimed to perform a meta-analysis in effort to assess the association between GSTP1 105IIe>Val gene polymorphism and the risk of BC. **Material and Methods:** A meta-analysis was conducted between May and July 2019. Papers were searched in Pubmed, Embase, Cochrane, and Web of Science and information of interest was extracted. The correlation and effect estimation were analyzed using random or fixed effect model. **Results:** We collected 17 studies consisting of 4.236 cases and 5.085 controls. Our pooled calculation revealed that GSTP1 105IIe>Val gene polymorphism was not associated with the risk of BC (OR 95%CI=1.11 [0.97-1.26], p=0.1190). We also performed sub-group analyses in accordance with ethnicity and genotyping method. In ethnicity sub-group, we failed to clarify the correlation between GSTP1 105IIe>Val gene polymorphism and the risk of BC both in Asian and Caucasian sub-groups. While, in genotyping method sub-groups, either using polymerase chain reaction (PCR) or PCR-Restriction fragment length polymorphism (PCR-RFLP) had no significant association with the risk of BC. **Conclusion:** There is no association between GSTP1 105IIe>Val gene polymorphism and the risk of BC.

Keywords: Bladder cancer; GSTP1; SNP; meta-analysis

ÖZET Amaç: Son 30 yılda, Glutatyon S-Transferaz P1 (GSTP1) 105IIe>Val mesane kanseri (MK) vakalarında yoğun olarak bildirildi. Fakat çalışmalar arasında çelişkili sonuçlar vardı. GSTP1 105IIe>Val gen polimorfizmi ve MK riski arasındaki ilişkiyi değerlendirmek için bir meta-analiz yapmayı amaçladık. **Gereç ve Yöntemler:** Mayıs ve Temmuz 2019 arasında meta-analiz yapıldı. Pubmed, Embase, Cochrane ve Web of Science'daki makaleler araştırıldı ve ilgili bilgiler alındı. Korelasyon ve etki tahmini rastgele veya sabit etki modeli kullanılarak incelendi. **Bulgular:** Toplam 4.236 olgu ve 5.085 kontrolü kapsayan 17 çalışmayı topladık. Toplanmış hesaplama GSTP1 105IIe>Val gen polimorfizminin MK riski ile ilişkili olmadığını ortaya koydu (OR %95 GA=1.11[0,97-1,26], p=0,1190). Ayrıca etnisite ve genotiplendirme yöntemine uygun olarak alt grup analizleri yaptık. Etnisite alt grubunda, hem Asyalı hem de vrupalı ırkta GSTP1 105IIe>Val gen polimorfizmi ile BK arasındaki korelasyonu açıklayamadık. Genotiplendirme yöntemi alt gruplarında, polimeraz zincir reaksiyonu (PCR) veya PCR-kısıtlama fragman uzunluğu polimorfizmi (PCR-RFLP) kullanarak MK ile ilişki bulmadık. **Sonuç:** GSTP1 105IIe>Val gen polimorfizmi ile MK riski arasında ilişki yoktur.

Anahtar Kelimeler: Mesane kanseri; GSTP1; SNP; meta-analiz

Bladder cancer (BC) was the 9th common malignancy worldwide. The report in 2012 found 429,793 new cases and 165,084 mortalities. However, the incidence varied between men and women, they revealed that the incidence in men is higher than in women.[1] Moreover, the incidence of BC may cor-

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relate to the risk factors of BC wherein, in developed countries, the smoking habit is still high.[2] Furthermore, several developed countries in Western Europe and North America, the countries with high incidence of BC, had high exposure to the carcinogenic substances from the work environment.[3] This might explain that the incidence of this disease had the trend to increase in seven countries, 11 countries had decreased trend, and the trend in 21 countries remained stable.[2] Therefore, it suggested that geographical factors related to the risk factors of BC and genetic factors might have a contribution to the development of BC.

Recently, the topic of gene-disease association studies had been widely investigated to describe a comprehensive understanding regarding the development of the disease. The existence of genetic variation in population with the same species make a population unique. Hence, studies have emerged to observe the effect of gene polymorphism in the disease. In the development of BC pathogenesis, it is globally known that bio-transformation enzymes such as Glutathione S-Transferase (GST), through detoxifying reactive chemical species, may play a pivotal role to regulate the development and the protection of BC.[4] One of GST single nucleotide polymorphisms (SNPs) widely reported in the case of BC is Glutathione S-Transferase P1 105Ile>Val (GSTP1 105Ile>Val). Briefly, GSTP1 is expressed due to the induction of reactive oxygen species (ROS) in the process of identifying the factor that may regulate the resistance to the certain hazardous chemical substances such as carcinogen, antitumor drugs, environment pollution, and product of ROS. Therefore, due to this mechanism, the GSTP 1 may govern the risk of BC. Since reported by Harris et al. in 1997 in UK population that the mutation of A>G allele on codon 105 exon 5 in the locus of GSTP1 gene had a significant association with the risk BC, the large scale of studies had been carried out to assess the correlation between this SNP and the risk of BC worldwide.[5] However, inconsistency was found across the studies. Furthermore, previous meta-analysis studies in this topic were also inconclusive and the quality of the previous meta-analyses, in genetic perspective, had no adequate power to conclude the association.

The aims of our current meta-analysis, therefore, was to assess the association between GSTP1 105Ile>Val gene variant and the risk of BC. In addition, our current meta-analysis applied more complex design in the genetic perspective than previous meta-analyses, and therefore our results were expected to provide more precise correlation between GSTP1 105Ile>Val gene polymorphism and the risk of BC.

MATERIAL AND METHODS

STUDY DESİGN

This present study was conducted from May to July 2019 to assess the correlation between the GSTP1 105Ile>Val gene variant and the risk of BC by calculating the combined odds ratio (OR) and 95% confidence interval (95%CI) using a random or fixed effect model. To attain our purpose, several previous studies reporting the association between GSTP1 105Ile>Val gene variant and the risk of BC were retrieved from Pubmed, Embase, Cochrane, and Web of Science. We employed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist to maintain the protocols of our study.[6]

LITERATURE SEARCH STRATEGY

A structured literature search, using specified search term, was carried out in Pubmed, Embase, Cochrane, and Web of Science to collect articles published up to 12th July 2019. The keywords used in our searching strategy were adapted from Medical Subject Heading (MeSH): (glutathione S-Transferase OR GST OR GSTP1 OR rs1695 OR IIe105val) AND (bladder OR urothelial) AND (carcinoma OR cancer OR Neoplasm). We also screened references list of previous meta-analysis or systematic review for new potentially relevant articles. We only included papers with larger sample size and more up-to-date if we found more than one article using the same data. To ensure data validation, our searching strategy was performed by three independent investigators (MI, AGS, YP).

STUDY ELIGIBILITY

The inclusion criteria were (1) articles with the following design: case-control, cross-sectional, cohort,

and randomized control trial; (2) assessing the correlation between GSTP1 105IIe>Val gene variant and the risk of BC; and (3) presenting genotype frequency for estimating OR95%CI. While, the exclusion was perfomed if the following criteria were found: (1) unrelated title and/or abstract; (2) review: (3) commentary; (4) unpublished studies; (5) non-standard data presentation; (6) low quality data; and (7) proven having deviation from Hardy-Weinberg Equilibrium (HWE).[7]

DATA EXTRACTION

The information of interest was extracted from included studies, including: (1) the first author name; (2) year of publication; (3) ethnicity of the population; (4) name of SNP; (5) genotyping method; and (6) genotype distribution of cases and controls for GSTP1 105IIe>Val gene polymorphism. Allele frequency was calculated from genotype frequency in accordance with Mendel's genetic law. Data extraction was performed by two independent investigators (MI, BD). If the discrepancy was found, a consensus was established.

COVARIATES AND SUB-GROUP ANALYSIS

To determine the correlation and effect estimates between GSTP1 105IIe>Val gene variant and the risk of BC, we performed a comprehensive analysis in all genetic models including alleles and genotypes of GSTP1 105IIe>Val gene variant. The genetic models were IIe *vs*. Val; Val *vs*. IIe; IIe/IIe *vs*. IIe/Val + Val/Val; IIe/Val *vs*. IIe/IIe+ Val/Val; and Val/Val *vs*. IIe/IIe +IIe/Val. Moreover, the sub-group analysis of genetic models according to ethnicity and genotyping method was performed. For ethnicity sub-group, data were catagorized based on regional of origin (Asian or Caucasian). While, for genotyping method sub-group, data were classified in accordance with the method used for gene identification: polymerase chain reaction (PCR) and polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP).

QUALITY ASSESSMENT

In our present study, each paper was assessed the quality using the Newcastle-Ottawa Scale (NOS) by three independent investigators. The three factors including the patients recruitment (4 points), the groups comparison (2 points), and the exposure (3 points) were used to assess the quality of each paper. The score of this quality assessment system ranged between zero (the worst) and 9 (the best). The score of each paper was assessed as good (≥ 7), moderate

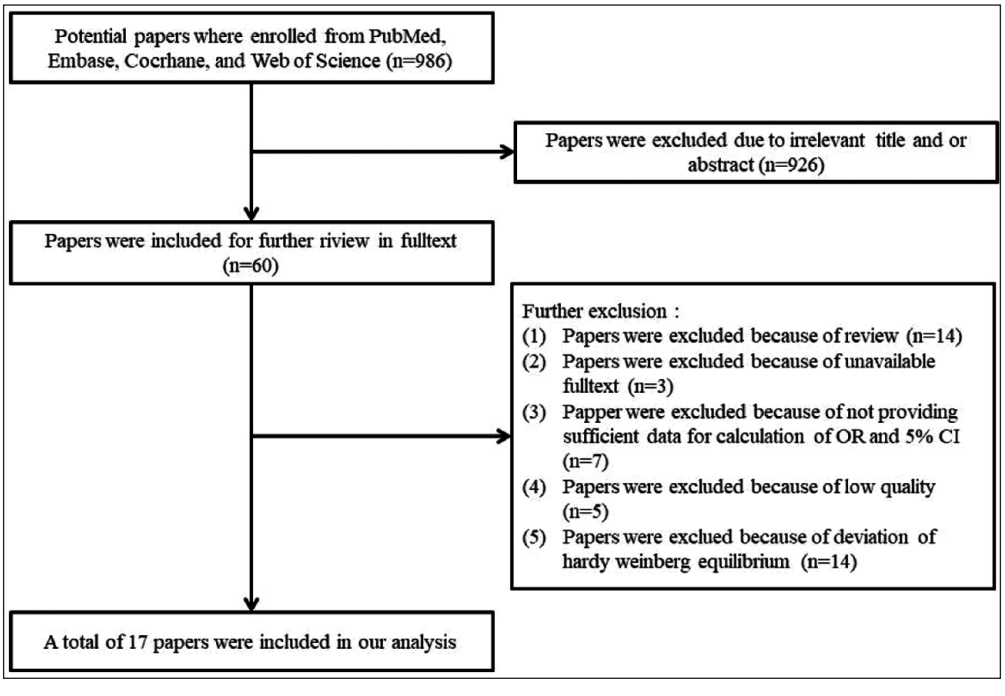

FIGURE 1: A flowchart of studies included in our meta-analysis.

(≥ 5), and poor (< 5).[8] If there was a discrepancy between the three independent investigators, we performed a consensus.

STATISTICAL ANALYSIS

The calculation of OR95%CI, determined by Z test, was used to assess the correlation between GSTP1 105IIe>Val gene variant and the risk of BC. The significant correlation was considered if we found the p-value of less than 0,05. Before determining the association, potential publication bias and heterogeneity were evaluated. For evaluating publication bias, we used Egger test. The publication bias was considered if the p-value of less than 0,05 was observed. For heterogeneity, we performed a Q test. The p value of less than 0.10 was considered having heterogeneity (random effect model). All statistical analyses in this study were conducted by three independent investigators using Comprehensive Meta-Analysis (CMA, New Jersey, USA) version 3.3 and Review Manager (Revman Cochrane, London, UK) version 5.3.

RESULTS

ELIGIBLE ARTICLES

Our search strategy in Pubmed, Embase, Cochrane, and Web of Science identified 986 articles assessing the correlation between GSTP1 105IIe>Val gene variant and the risk of BC. Of which, because of unrelated title and or abstract, we excluded 926 papers. Furthermore, we also excluded 43 papers because of review (14 papers), unavailable full text (3 papers), not providing sufficient data (7 papers), poor quality (5 papers), and deviation from HWE (14 papers). Finally, a total of 17 papers were compatible for our meta-analysis. Figure 1 describes the flowchart of the eligibility pathway in our study, and the baseline characteristics of compatible papers in our analysis are provided in Table 1.

DATA SYNTHESIS

We collected 17 studies consisting of 4,236 cases and 5,085 controls. Of those, 13 studies failed to confirm the association between GSTP1 105IIe>Val gene variant and the risk of BC, and the association was found by four other studies.[5,9-24] Our pooled calculation revealed that, overall, GSTP1 105IIe>Val gene variant was not correlated with the risk of BC (OR95%CI = 1.11 [0.97–1.26], p = 0.1190). Moreover, we also performed sub-group analyses in accordance with ethnicity and genotyping method. In ethnicity sub-group, we also failed to clarify the association between GSTP1 105IIe>Val gene variant and the risk of BC both in Asian and Caucasian sub-groups. While, in genotyping method sub-group, either using PCR or PCR-RFLP, no significant association was also observed between GSTP1 105IIe>Val gene variant and the risk of BC. The forest plots showing the correlation between GSTP1 105IIe>Val gene variant and the risk of BC are shown in Figure 2 for Val *vs*. IIe and Figure 3 for Val/Val *vs*. IIe/IIe + IIe/Val. A summary of ORs and 95%CIs regarding the correlation between the GSTP1 gene variant and the risk of BC is described in Table 2.

EVIDENCE OF HETEROGENEITY AND POTENTIAL PUBLICATION BIAS

In our whole data, the evidence of heterogeneity was found in all alleles and genotypes of GSTP1 105IIe>Val gene polymorphism. Therefore, we used a random effect model to assess the correlation. In Asian sub-group analysis, random effect model was used to assess the analysis in all genetic models. In Caucasian sub-group, IIe/Val and Val/Val genotypes were evaluated using fixed effect model due to no evidence of heterogeneity, while we, because of heterogeneity, used random effect model to analyze all alleles and IIe/IIe genotype. In PCR sub-group, all genetic models, except IIe/Val, were evaluated using random effect model. While, in PCR-RFLP sub-group, random effect model was used to assess all genetic models. Moreover, for evaluating publication bias, we did not find publication bias on our source studies. The publication bias also was not found on both sub-group analyses, both ethnicity and genotyping method sub-groups. We summarize the Egger test of GSTP1 105IIe>Val gene polymorphism in Table 3.

DISCUSSION

Our findings confirmed that neither valine nor IIe allele was associated with the risk of BC. There were some previous meta-analysis studies which assessed

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

	Case								Control										
Author & year	**Ile/Ile**	**Ile/Val**	**Val/Val**	**N**	**Ile**	**Val**	**n**	**x2 HWE**	**Ile/Ile**	**Ile/Val**	**Val/Val**	**N**	**Ile**	**Val**	**n**	**x2 HWE**	**Country**	**Ethnicity**	**Genotyping method**
Altayli et al. 2009	75	46	14	135	196	74	270	2.79	62	58	8	128	182	74	256	1.34	Turkey	Caucasian	PCR-RFLP
Altunkol et al. 2018	38	19	3	60	95	25	120	0.10	34	21	5	60	89	31	120	0.45	Turkey	Caucasian	PCR-RFLP
Broberg et al. 2005	24	27	10	61	75	47	122	0.26	71	69	15	155	211	99	310	0.09	Sweden	Caucasian	PCR
Fontana et al. 2009	20	27	4	51	67	35	102	1.55	28	13	4	45	69	21	90	1.67	French	Caucasian	PCR
Garcia-closas et al. 2005	486	525	130	1141	1497	785	2282	0.43	488	531	119	1138	1507	769	2276	2.09	Spain	Caucasian	PCR
Harries et al. 1997	25	32	14	71	82	60	142	0.41	79	66	10	155	224	86	310	0.60	UK	Caucasian	PCR
Hsu li. et al. 2008	164	45	2	211	373	49	422	0.32	149	64	5	218	362	74	436	1.05	China	Asian	PCR-RFLP
Hung et al. 2004	103	77	21	201	283	119	402	1.31	112	78	24	214	302	126	428	3.22	Italy	Caucasian	PCR-RFLP
Kopps et al. 2008	66	56	21	143	187	99	286	2.44	82	82	31	196	247	145	392	1.84	German	Caucasian	PCR
Lesseur et al. 2012	294	289	75	658	877	439	1316	0.10	411	414	103	928	1236	620	1856	0.01	US	Caucasian	PCR
Ma et al. 2002	33	27	1	61	93	29	122	2.99	110	59	10	179	279	79	358	0.31	China	Asian	PCR
Min-Yuan et al. 2008	301	274	82	657	876	438	1314	2.50	284	327	73	684	895	473	1368	2.20	US	Caucasian	PCR-RFLP
Mittal et al. 2005	33	57	16	106	123	89	212	1.14	95	61	6	162	251	73	324	1.00	India	Asian	PCR-RFLP
Pandith et al. 2013	129	45	6	180	303	57	360	0.69	159	48	3	210	366	54	420	0.08	India	Asian	PCR-RFLP
Reszka et al. 2014	116	109	19	244	341	147	488	0.91	160	166	39	365	486	244	730	0.17	Poland	Caucasian	PCR
Steinhoff et al. 2000	67	59	9	135	193	77	270	0.70	70	46	11	127	186	68	254	0.74	German	Caucasian	PCR-RFLP
Toruner et al. 2001	67	42	12	121	176	66	242	1.89	83	33	5	121	199	43	242	0.54	Turkey	Asian	PCR-RFLP

HWE: Hardy Weinberg Equilibrium; PCR: Polymerase Chain Reaction; PCR-RLFP: Polymerase Chain Reaction - Restriction Fragment Length Polymorphism.

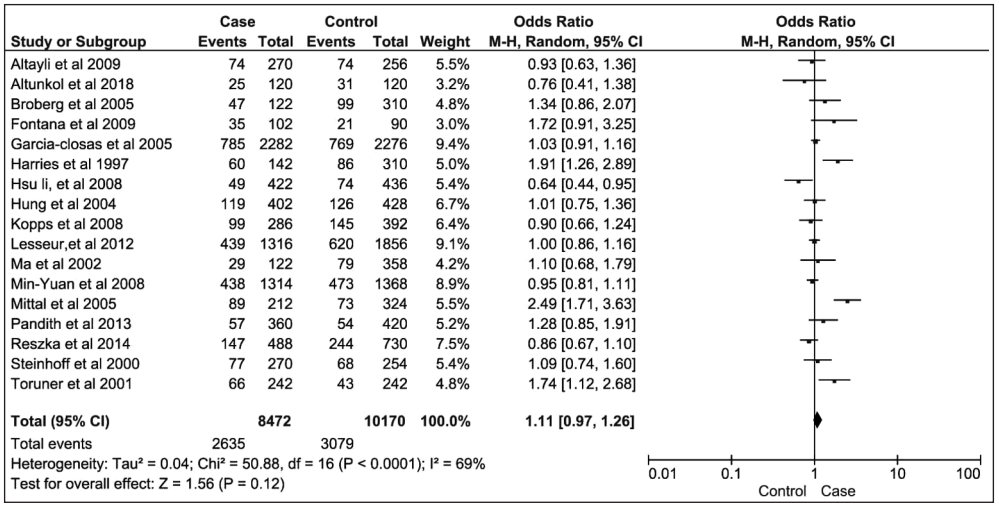

FIGURE 2: Forest plot of the association between GSTP1 gene polymorphism and the risk of bladder cancer (Val vs. Ile).

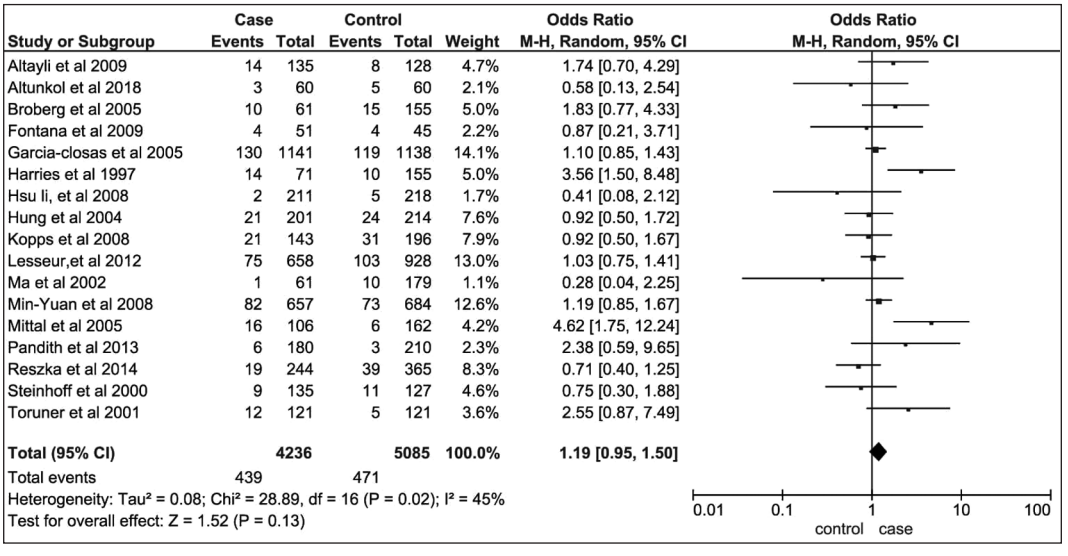

FIGURE 3: Forest plot of the association between GSTP1 gene polymorphism and the risk of bladder cancer (ValVal vs. IleIle + ValVal).

the association between the risk of BC and GSTP1 105IIe>Val gene polymorphism.[25-28] Our results were contrast with the earlier meta-analyses conducted by Kellen et al, Wu et al, and Wang et al., but were consistent with Yu et al.[25-28] The emphasize of our current study applied on HWE, while other studies focused on the number of studies, cases, and control that included in their meta-analyses. The HWE is the basis of population genetics. The law proposes that, in a large random mating population, the genotype frequencies are functions of allele frequencies, and they should remain constant over the periods. The significant deviation from HWE, therefore, could show a violation of HWE principle in the general population. However, other possible sources such as population stratification and genotyping errors could also lead to the violation. In this case, the conclusion could be biased if unchecked.[29] Our studies excluded studies which violated from HWE. However other meta-analysis studies still included the studies with HWE deviation. Therefore, our present study was considered to have better quality from the genetic study perspective. The Table 3 consists of the summary of the previous meta-analyses and their limitations.

TABLE 2: Summary of the association between GSTP1 Ile105val gene polymorphism and the risk of bladder cancer.

			Ethnicity		Genotyping	
Models	**Parameters**	**Overall**	**Caucasian**	**Asian**	**PCR**	**PCR-RFLP**
Ile vs. Val	OR	0.90	0.98	0.76	0.93	0.90
	95%CI	0.79-1.03	0.89-1.08	0.47-1.22	0.80-1.07	0.70-1.14
	P	0.1190	0.7880	0.2570	0.2920	0.3830
	pH	<0.0001	0.0980	<0.0001	0.0330	<0.0001
	pE	0.207	0.0960	0.4970	0.1390	0.3170
Val vs. Ile	OR	1.11	1.02	1.32	1.08	1.11
	95%CI	0.97-1.26	0.93-1.13	0.82-2.11	0.94-1.25	0.87-1.42
	P	0.1190	0.6600	0.2570	0.2920	0.3830
	pH	<0.0001	0.0980	<0.0001	0.0330	<0.0001
	pE	0.2070	0.0960	0.4970	0.1390	0.3170
Ile/Ile vs. Ile/Val + Val/Val	OR	0.90	1.02	0.71	0.92	0.91
	95%CI	0.77-1.06	0.93-1.12	0.41-1.22	0.78-1.10	0.67-1.22
	P	0.2140	0.6550	0.2230	0.3720	0.5190
	pH	<0.0001	0.1070	<0.0001	0.0800	<0.0001
	pE	0.2550	0.1250	0.5640	0.1550	0.3880
Ile/Val vs. Ile/Ile + Val/Val	OR	1.03	0.95	1.24	1.00	1.01
	95%CI	0.90-1.17	0.87-1.04	0.84-1.84	0.90-1.12	0.79-1.29
	P	0.7210	0.2450	0.2830	0.9110	0.9440
	pH	0.0140	0.1780	0.0160	0.2810	0.0060
	pE	0.1780	0.1040	0.3690	0.0830	0.2840
Val/Val vs. Ile/Ile + Ile/Val	OR	1.19	1.09	1.60	1.10	1.33
	95%CI	0.95-1.50	0.95-1.26	0.61-4.18	0.83-1.47	0.89-2.00
	P	0.1280	0.2250	0.340	0.5030	0.1610
	pH	0.0250	0.2230	0.0390	0.0750	0.0610
	pE	0.2810	0.1460	0.7210	0.2540	0.3900

GSTP1: Gluthation S-Transferase P1; OR: Odd ratio; CI: Confidence interval; Ph: p heterogeneity; pE: p Egger.

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

Author & year	**Case setting**	**SNP**	**NS**	**Main Result**	**Limitations**
Kellen et al 2007	Bladder cancer	GSTP1	16	GSTP1 had assocation with the risk of bladder cancer	Five studies did not conform with HWE Two studies were unavailable fulltext
Wang et al 2013	Bladder cancer	GSTP1	25	GSTP1 had assocation with the risk of bladder cancer	Nine studies did not conform with HWE One study was unavailable fulltext
Wu et al 2016	Bladder cancer	GSTP1	20	GSTP1 had assocation with the risk of bladder cancer	Six studies did not conform with HWE One study was unavailable fulltext
Yu et al 2012	Bladder cancer	GSTA1,GSTM1, GSTP1, GSTT1	23	GSTP1 had no assocation with the risk of bladder cancer	Seven studies did not conform with HWE One study was unavailable fulltext

GSTP1: Gluthation S-Transferase P1; GSTA1: Gluthation S-Transferase A1; GSTM1: Gluthation S-Transferase M1; GSTT1: Gluthation S-Transferase T1; SNP: Single nucleotide polymorphism; NS: Number of studies; HWE: Hardy weinberg equilibrium.

Theoretically, the precise mechanism bridging between GSTP1 105IIe>Val gene variant and the risk of BC is complex. Briefly, GSTP, one of GST superfamily, protects the normal cell against alkylating agent such as carcinogen and pharmacologically active compounds. The GSTP neutralizes the electrophilic site of alkalyting agent by glutathione (GSH) conjugation.[30,31] The gluthathione conjugate are metabolized further through the mercapturic acid pathway, and their metabolites are excreted through urine.[32] The conjugation process predominanly occurs in the bladder uroephithelium. Moreover, previous study reported that GSTP1 was proven to decrease the catalyzing activity of GST. Hence, through this mechanism, GSTP1 may have a pivotal role for decreasing the risk of BC.[33] However, our meta-analysis failed to support the theory concerning the direct involvement of GSTP1 105IIe>Val gene polymorphism on BC. Our study also was unable to yet explain this incompatibility, but several reasons might contribute to this finding. Genetic alteration of GSTP1 alone may not directly affect the pathogenesis of BC, but other factors such as undiscovered gene-gene interaction and gene-environment complexity may correlate to GSTP1 enzyme regulation and BC. Moreover, the over-expression of GSTP1 was observed on BC that induced by anti-apoptosis agent, and the over-expression of GSTP1 was found to link to stress signaling and resistance of apoptosis mechanism.[34-37] This suggested that apoptosis agent also had the important role for influencing the effect of GSTP1 on BC. In our perspective, it was proposed that the pathogenesis of BC might be complex and it might involve several factors, not a single factor like GSTP1 105IIe>Val gene polymorphism alone. Therefore, studies are needed to elucidate the concise mechanism how GSTP1 105IIe>Val gene polymorphism affects BC.

Sub-group analysis was performed in this study. It consisted of ethnicity and genotyping method subgroups. Our results were consistent with our main findings that there was no significant association between allele and genotype polymorphism on GSTP1 105IIe>Val and BC in different ethnicities and genotyping methods. In previous meta-analysis, Kellen et al. compared Asian, Europe, and American ethnicity and they found an increased OR value on IIe/Val and Val/Val genotypes only in Asian ethnicity.[25] Our results also showed the increased OR value on Asian ethnicity, but it was not statistically significant. However, our ethnicity sub-groups analysis was similar to that of Yu et al.[28] The difference in OR might be influenced by the frequency of alleles and genotypes of GSTP1 105IIe>Val in Asian, Caucasian, and African ethnicities.[38] For example, a study found that the Val/Val genotype frequency in Caucasian was lower than in other ethnicity, which was only in 5% of Caucasian.[39] Furthermore, in the genotyping method subgroup, we also failed to find the association between GSTP1 105IIe>Val and BC. Our findings confirmed that there was no significant difference in the interpretation of the data between PCR and PCR-LFP genotyping method.

To the best of our knowledge, the association between GSTP1 105IIe>Val gene variant and the risk of BC remained inconclusive both in previous real studies and meta-analyses. The inconclusive association rose the dilemma for the physicians and researchers. Therefore, because previous meta-analyses had several crucial limitations, our present study reported meta-analysis with eliminating the crucial limitations of previous studies, and our findings emphasized that no association was observed between GSTP1 105IIe>Val gene variant and the risk of BC. Compared to previous meta-analyses, in the genetic perspective, our current study might provide more powerfull association between GSTP1 105IIe>Val gene polymorphism and the risk of BC. Our findings showed the expected results, despite the basic theory showed that there was over-expression on the GTSP1 105IIe>Val gene on BC. Maybe, the gene-gene and gene-environment interaction could be assessed if the risk factors, the research confoundings, or other SNP assays were provided in upcoming studies. Other clinical benefits might be achieved if the study of GSTP1 105IIe>Val gene polymorphism could be expanded in other diseases such as thyroid, colorectal, or neck cancer which had a higher protein expression according to immunohistochemistry assay.[40]

Several important limitations were observed in our meta-analysis. First, our data did not involve the

risk factors of BC. Second, the possibility of gene-gene and gene-environment interaction in this context was not evaluated. Third, our data were obtained from the case-control study. In the near future, the better study design may be considered in genetic study to obtain more powerful association. Finally, our study had a relatively small sample size compared to the other meta-analyses.

CONCLUSION

Our meta-analysis concludes that there is no clear correlation between GSTP1 105IIe>Val gene polymorphism and the risk of BC. Moreover, we also failed to show the association in our sub-group analyses, either in ethnicty and genotyping method sub-groups. In genetic prespective, compared to previous meta-analysis, our study may provide better corelation and our meta-analysis emphasizes that GSTP1 105IIe>Val gene variant does not affect the risk of BC. Our meta-analysis may contribute to better understanding between GSTP1 105IIe>Val gene variant and the risk of BC.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

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: *Muhammad Ilmawan;* ***Design:*** *Muhammad Ilmawan;* ***Control/Supervision:*** *Muhammad Ilmawan, Besut Daryanto, Atma Gunawan, Jonny Karunia Fajar;* ***Data Collection and/or Processing:*** *Muhammad Ilmawan, Avan Guntur Satriawan, Jonny Karunia Fajar;* ***Analysis and/or Interpretation:*** *Muhammad Ilmawan, Bagus Aulia Mahdi, Fredo Tamara;* ***Literature Review:*** *Muhammad Ilmawan, Avan Guntur Satriawan, Yeni Purnamasari;* ***Writing the Article:*** *Muhammad Ilmawan, Avan Guntur Satriawan, Yeni Purnamasari;* ***Critical Review:*** *Muhammad Ilmawan, Besut Daryanto, Atma Gunawan Jonny Karunia Fajar.*

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