RESEARCH ARTICLE

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GSTP1 rs1695 Variant and Colorectal Cancer Risk in Women Aged 50+: Insights from Iran's Largest Cohort and Meta-Analysis

Monirossadat Haerian[1,2], Batoul Sadat Haerian[1]*, Hassan Mehrad-Majd[3], Saadat Molanaei[4], Farid Kosari[5], Shahram Sabeti[6], Farahnaz Bidari-Zerehpoosh[6], Ebrahim Abdolali[7]

Abstract

Objective: To evaluate the association between *GSTP1* rs1695 A>G polymorphism and colorectal cancer (CRC) risk in an Iranian cohort, and to validate findings through a systematic review and meta-analysis. **Methods:** A multicenter case-control study was conducted in Tehran hospitals, including CRC patients and matched controls. Demographic and clinical data were collected, and DNA was extracted from FFPE tissues and blood. Genotyping of *GSTP1* rs1695 was performed using TaqMan® real-time PCR, with 5% of samples validated by direct sequencing. Logistic regression adjusted for age and gender was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs), with Bonferroni correction applied. A systematic review and meta-analysis was performed following PRISMA guidelines using five databases, including studies up to January 2025. **Results:** The study included 2,590 participants (1,038 CRC cases). CRC incidence was higher in individuals aged ≥50 years, with no significant gender difference. Colon cancer was more common, and most tumors were moderate or well differentiated at stages II–III. The GA genotype of *GSTP1* rs1695 was significantly associated with increased CRC risk ($p = 0.013$), especially in those aged ≥50 years ($p = 0.003$). The combined AA + AG genotypes were also associated with increased risk ($p = 0.016$). Among females, the G allele showed higher CRC susceptibility, especially in older age ($p = 0.0001$). The meta-analysis of 30 studies (21,376 individuals) showed no overall association between rs1695 and CRC risk, but Iranian subgroup data indicated a modest association in AG vs. GG and AA+AG vs. GG models, which lost significance after Bonferroni correction. No publication bias was detected. **Conclusion:** The Iranian cohort showed an age- and gender-specific association between *GSTP1* rs1695 and CRC risk. However, the meta-analysis did not support a consistent link, suggesting possible population-specific effects.

Keywords: Colorectal cancer- *GSTP1* rs1695 polymorphism- susceptibility variant- meta-analysis

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Introduction

Colorectal cancer (CRC) is the third most common cancer by incidence and the second leading cause of cancer-related mortality worldwide [1, 2]. The incidence and mortality rates of CRC differ significantly across populations due to a combination of genetic, environmental, and their combination. Genetic background, particularly specific risk alleles and mutations, plays a crucial role in influencing CRC susceptibility. Evidence has identified over 200 common genetic variants associated with CRC risk, underscoring the complex and multifactorial genetic architecture of this disease [3, 4]. Understanding these genetic factors is critical for developing personalized prevention strategies, improving early detection, and advancing targeted therapies for CRC.

Among the genetic variants implicated in CRC, the exonic *GSTP1* rs1695 A > G variant (located at 11q13.2: 67585218) or Ile105Val has garnered significant attention due to its association with various diseases, including CRC [5]. *GSTP1* or Glutathione S-Transferase Pi 1 is a member of the GST superfamily, which encodes phase II metabolic enzymes responsible for detoxifying a wide range of harmful compounds, such as drugs and carcinogens [6]. Recent studies have highlighted the potential role of the *GSTP1* rs1695 variant in increasing CRC risk [7]. The

*[1]Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran. [2]Food and Drug Control Reference Laboratories, Ministry of Health and Medical Education, Tehran, Iran. [3]Clinical Research Development Unit, Ghaem Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. [4]Department of Pathology, Milad Hospital, Tehran, Iran. [5]Department of Pathology, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran. [6]Department of Pathology, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran. [7]Department of Pathology, Taleghani Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran. *For Correspondence: batoolsadat@yahoo.com*

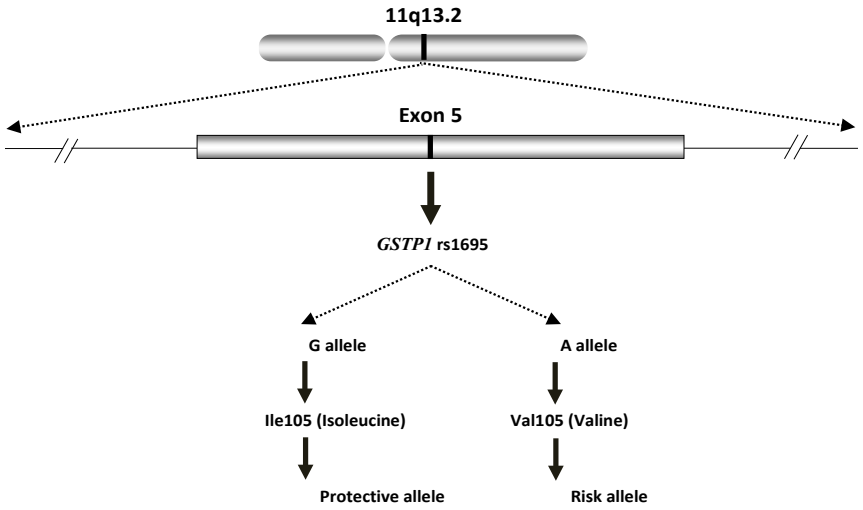

Figure 1. The rs1695 Polymorphism is Located in Exon 5 of the *GSTP1* Gene. The G allele results in reduced enzyme activity, potentially leading to impaired detoxification of carcinogens and an increased susceptibility to cancer.

substitution of the A allele to G results in exon 5 of the *GATP1* gene results in a change of Isoleucine to Valine at position 105 within the active site, located at the C-terminal domain of the protein (Figure 1). This region is critical for binding to substrate and catalytic efficiency of the enzyme [8]. Therefore, Alteration of alleles modifies the hydrophobic binding pocket of the enzyme, potentially impairing its ability to effectively detoxify electrophilic compounds, including carcinogens and toxins. Reduction of enzymatic activity may results in the accumulation of these toxic compounds, thereby increasing susceptibility to various cancers, including CRC. This underscores the critical role of this variant in the pathogenesis of the disease [9, 10].

Investigating the potential of *GSTP1* rs1695 A > G as a risk variant for CRC in the Iranians from the Middle East population could provide valuable insights into the genetic mechanisms underlying CRC in this region. While limited studies have been conducted on this population, their small sample sizes raise the possibility of type II errors, which may impact the reliability of the findings. To address this gap, this study aims to determine whether this variant is a genetic marker for CRC susceptibility in a cohort of 2,590 individuals, 40% of whom are affected by CRC, representing the largest study of Iran. Additionally, a meta-analysis of the pooled data from previous studies with this cohort will further elucidate the role of this variant in CRC development, potentially informing targeted prevention and therapeutic strategies.

Materials and Methods

Case-control study

This study is part of a multicentre cooperation between the Milad, Loghman Hakim, Sina, and Taleghani hospitals. The research protocol was approved by the Ethics Committees of all centres for recruiting both cases and controls. The inclusion and exclusion criteria have been detailed in a previous report [11]. Written informed consent was given by all patients or by their guardians in the case of a child. A standardized extraction template was administered to collect demographic details and information on clinical, medical, and pathological history from the medical records. Controls, who had no history of cancer, were age- and gender-matched and recruited from hospital admissions for trauma. DNA samples from patients and controls were extracted from formalin-fixed paraffin-embedded (FFPE) tissues and peripheral blood collected in EDTA vacuum tubes, respectively.

Genotyping of *GSTP1* rs1695 was performed using a TaqMan® SNP Genotyping Assay (Assay ID: C__3237198_20, Applied Biosystems), which includes a primer pair flanking the SNP region and two allele-specific probes labeled with VIC and FAM. To ensure accuracy, 5% of the samples were re-genotyped via Sanger sequencing. Hardy-Weinberg equilibrium (HWE) was tested for the genotypes. Continuous data (e.g., CRC onset age) were presented as mean ± standard deviation (SD), while categorical data (e.g., gender, tumor location, grade, stage, genotypes, and alleles) were expressed as frequencies. Statistical analyses were conducted using the Chi-square test and t-test to assess differences in categorical and continuous variables, respectively. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to evaluate the association between the rs1695 allele/genotype and CRC risk. Statistical significance was determined using two-sided p-values (<0.05), analyzed with the SPSS software package (version 15.0; SPSS, Chicago, IL, USA).

Meta-analysis

The current systematic review and meta-analysis were done on the basis of the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)" protocol [12]. The Mesh terms for searching were "colorectal cancer," "colon cancer," "rectal cancer," "polymorphism," "variant," "*GSTP1*," "rs1695," and "susceptibility" in the MEDLINE, Scopus, Embase, Cochrane library, and ScienceDirect databases with no language limitation published till January 2025.

References of the papers were hand searched for finding other related data. The exclusion and inclusion criteria and meta-analysis method were the same as our previous report [11]. Bonferroni correction was used for reduction of type I error or false positive results of both case-control study and meta-analysis [13].

Results

Case-control study

In this case-control study, a total of 2,590 participants were recruited from four hospitals in Tehran, with 40% (N = 1,038) being CRC patients (Table 1). The mean age at CRC diagnosis was significantly different between cases and controls (58 ± 15 vs. 59 ± 10, respectively; p = 0.026). The majority of both cases and controls were aged 50 years or older compared to those under 50 (OR = 0.69, 95% CI = 0.57–0.84). A significant difference was observed between cases and controls based on the age groups (< 50 vs. ≥ 50 years, P < 0.01). While CRC was more common in males than females (57% vs. 43%), no significant difference in gender distribution was observed between cases and controls (p = 0.913).

Among the patients, colon cancer was significantly more prevalent than rectal cancer (77% vs. 23%; p < 0.01). Based on histological differentiation, 88% of tumor samples were classified as moderate or well-differentiated. At the time of diagnosis, tumor node metastasis (TNM) staging revealed that 11%, 42%, 44%, and 3% of cases were at stages I, II, III, and IV, respectively. The distribution of histological differentiation and TNM stages varied significantly between I+II vs. III+IV among the patients (p < 0.01).

Distribution of genotypes of controls was consistent with HWE (p > 0.05)

The *GSTP1* rs1695 variant showed a significant association with colorectal cancer risk for the GA genotype (OR = 1.43, 95% CI = 1.08–1.91, unadjusted P = 0.014), indicating a moderately increased risk compared to the reference GG genotype. The AA genotype displayed a marginal association (OR = 1.31, 95% CI = 0.99–1.74, unadjusted P = 0.059). At the allele level, no significant differences were observed, as the A allele frequency was very similar between CRC cases (71%) and controls (72%) (OR = 1.05, 95% CI = 0.88–1.25, unadjusted P = 0.591).

An adjusted association study of the rs1695 variant and CRC risk by gender and age of CRC onset was conducted using binomial logistic regression (Table 2). After applying the Bonferroni correction for multiple testing, significant associations were observed, underscoring the critical role of the *GSTP1* rs1695 polymorphism in CRC risk across sex subgroups. In the overall population, individuals with the AG genotype showed an increased risk of CRC (OR = 1.45, 95% CI: 1.08–1.93, p = 0.013), as did those with combined AA + AG genotypes (OR = 1.37, 95% CI: 1.04–1.80, p = 0.023). Elevated risks were particularly evident in individuals aged 50 or older, especially among those with the AG genotype (OR = 1.63, 95% CI: 1.18–2.26, p = 0.003) or combined AA + AG genotypes (OR = 1.45,

Table 1. Demographic, Genotypic, and Allelic Characteristics of Iranian Patients and Matched Controls (N = 2,590)

Characteristics	Patient (N = 1038)	Control (N = 1552)	OR (95%CI)	p
Mean age at diagnosis, Mean (SD)	58 (15)	59 (10)	-	0.026
Age group, N (%)				
< 50	288 (28)	326 (21)	-	Ref.
≥ 50	750 (72)	1226 (79)	0.69 (0.57-0.84)	< 0.01
Gender, N (%)				
Females	447 (43)	591 (43)	-	Ref.
Males	665 (57)	887 (57)	0.99(0.85-1.61)	0.913
Tumor location, N (%)				
Colon	774 (77)	-	-	Ref.
Rectum	237 (23)	-	-	< 0.01
Grade, N (%)				
Poor	111 (12)	-	-	Ref.
Moderate+Well	856 (88)	-	-	<0.01
TNM, N (%)				
I+ II	492 (53)	-	-	Ref.
III+IV	440 (47)	-	-	<0.01
GSTP1rs1695, N (%)				
AA	548 (53)	811 (52)	-	Ref.
GA	382 (37)	619 (40)	1.43 (1.08-1.91)	0.014
GG	108 (10)	122 (8)	1.31 (0.99-1.74)	0.059
A	1478 (71)	2241 (72)	-	Ref.
G	598 (29)	863 (28)	1.05 (0.88-1.25)	0.591

Abbreviations: TNM, Tumor, Node, Metastases; OR, odds ratio; CI, confidence interval

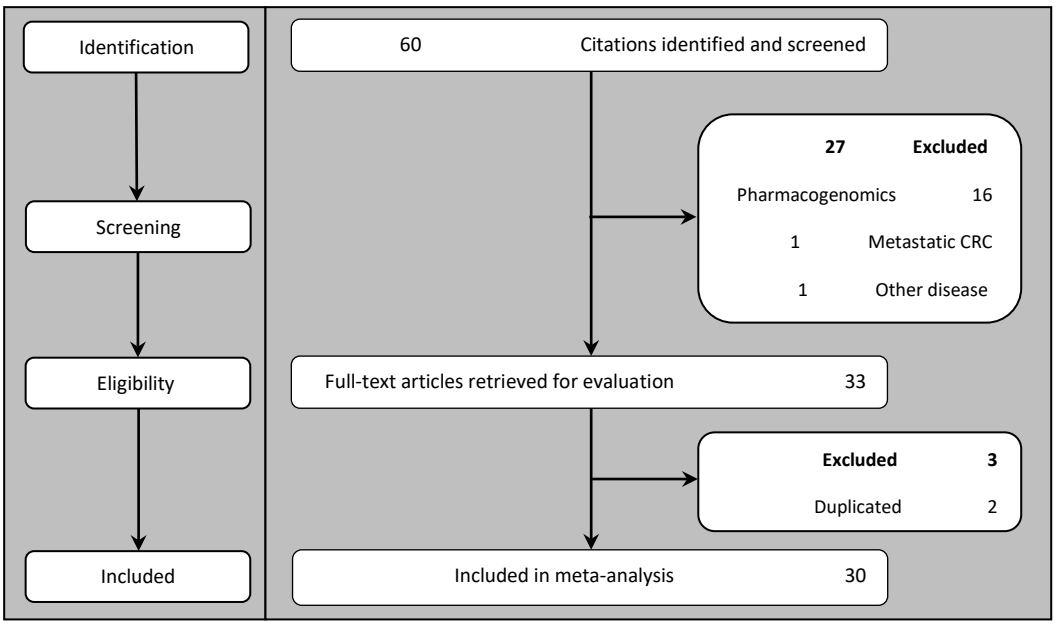

Figure 2. Process of Searching and Screening of the Studies

95% CI: 1.07–1.97, p = 0.016).

In females, the presence of the G allele was significantly associated with increased CRC susceptibility compared to the control group (OR = 1.46, 95% CI: 1.13–1.90, p = 0.004). Furthermore, when comparing females to males in the CRC group, women exhibited a notably higher risk of CRC than men (OR = 1.68, 95% CI: 1.29–2.21, p = 0.0001). The GG genotype in females aged 50 or older with CRC was more frequentl than than AA + AG compared with controls (14% vs 10% and 86% vs 90%, respectively) in controls. These findings highlight the influence of age and sex factors on genetic risk for CRC, emphasizing the role of the *GSTP1* rs1695 polymorphism in shaping individual susceptibility, particularly among Iranian women aged 50 or older.

Meta-analysis

A comprehensive search and selection of online data relevant to the *GSTP1* rs1695 variant in CRC identified 30 eligible studies published between 1997 and 2019 for inclusion in the meta-analysis (Figure 2, Table 3). These studies include key publications [14-42]. Of these studies, 23%, 67%, and 10% originated from Asian, Caucasian, and mixed populations, respectively, and 77% of the studies adhered to HWE for their control genotypes. Data from these 30 studies, combined with the present case-control study, comprised a total of 21,376 subjects (9,374 cases and 12,002 controls) with an average sample size of 690 (ranging from 146 to 2,590).

The meta-analysis was conducted both overall and across Asian, Caucasian, and mixed ethnic groups. The meta-analysis results did not reveal a significant association between the rs1695 variant and CRC risk in the overall analysis or in the Asian, Caucasian, and mixed subgroups (p > 0.05) (Table 4, Figure 3). However, a subsidiary meta-analysis of pooled data from Iranian studies suggested an association under the genotype models AG vs. GG (OR = 0.70, 95% CI 0.53-0.93, pEffecetive = 0.01, I2 = 0%, pHeterogeneity = 0.87) and AA+AG vs. GG (OR = 0.74, 95% CI 0.57-0.96, pEffecetive = 0.02, I^2 = 0%, pHeterogeneity = 0.87). Following applying the Bonferroni correction for multiple comparisons (p = 0.001), these associations did not remain significant.

The funnel plot for rs1695 (A vs. G) was symmetric, and Egger's test indicated no significant asymmetry, suggesting the absence of publication bias [interceptOR = 0.79 (-0.45, 2.04), p = 0.20] (Figure 4). Therefore, the meta-analysis results did not confirm the contribution of the rs1695 polymorphism to CRC susceptibility in the overall populations or in subgroup analyses by ethnicity.

Discussion

This study provides key insights into the relationship between the *GSTP1* rs1695 polymorphism and CRC susceptibility through a rigorous case-control investigation and meta-analysis. Utilizing a cohort of 2,590 participants from Iran, the findings revealed significant associations between the *GSTP1* rs1695 variant and CRC risk, with marked differences observed in sex- and age-stratified analyses. Specifically, older age amplified the impact of genetic polymorphisms, with stronger associations between these variants and CRC susceptibility observed in females aged 50 years or older. These results underscore the critical role of genetic factors in CRC risk, particularly in older women, and highlight the importance of incorporating both age and sex into genetic risk assessments and preventive strategies.

The G allele and GG genotype were found to significantly elevate CRC risk in females, particularly those aged 50 or older, compared to other age and gender groups. This is consistent with findings from both control and CRC populations. The GG genotype is associated with reduced *GSTP1* enzyme activity, impairing the detoxification of carcinogens and oxidative

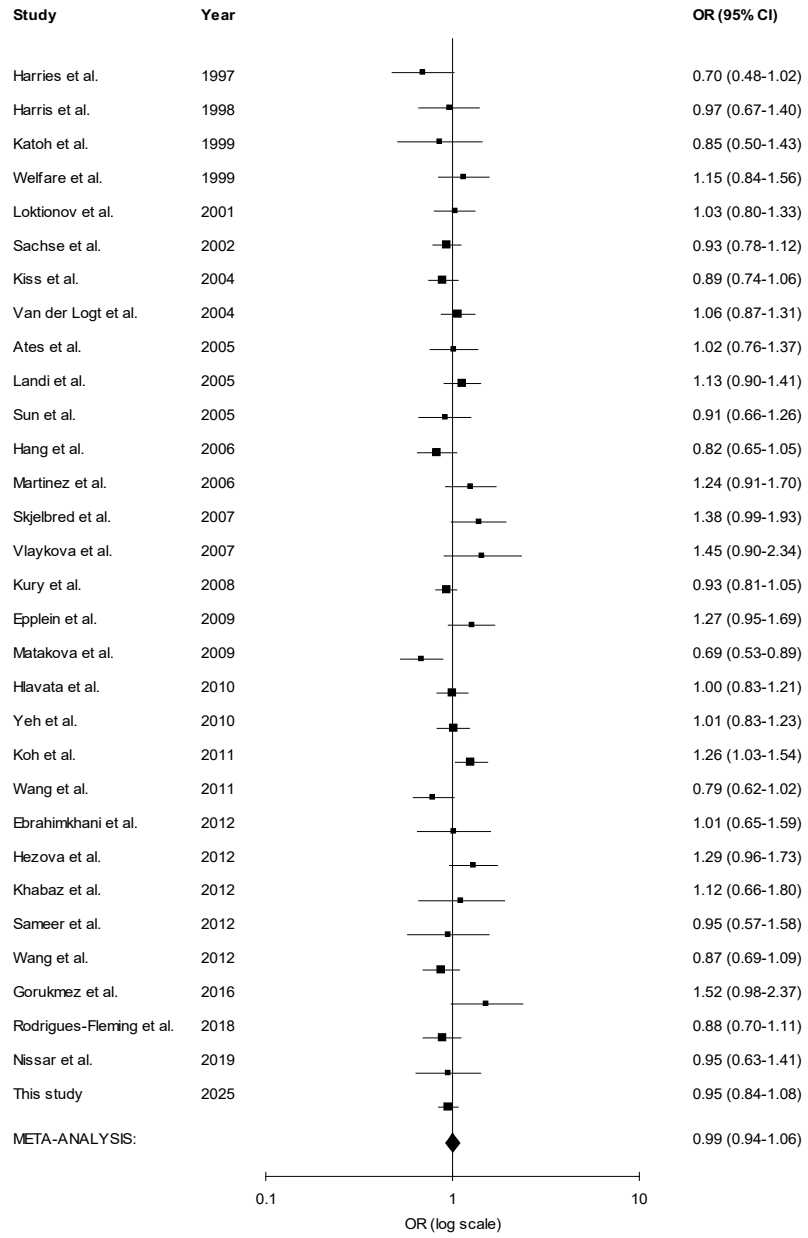

Figure 3. Forest Plot of A vs. G of GSTP1 rs1695 and Susceptibility to CRC in Overall of Studies

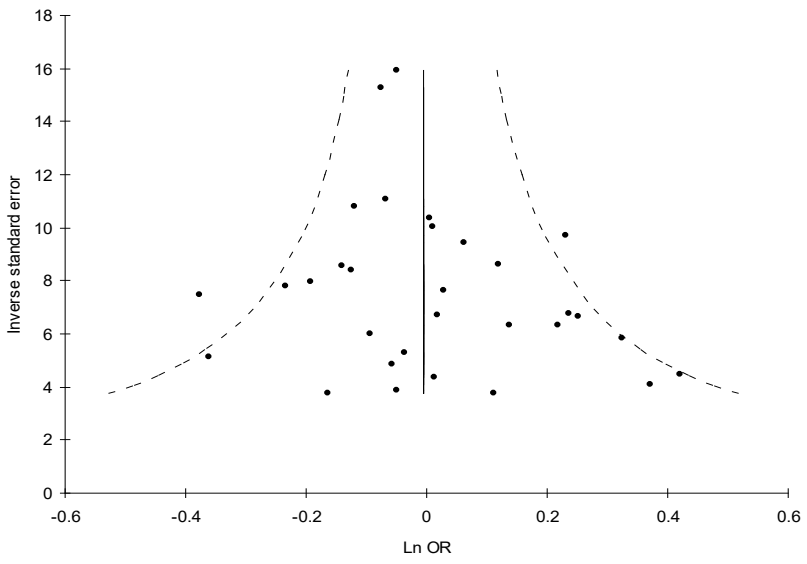

Figure 4. Funnel Plot of A vs. G of *GSTP1* rs1695 and Susceptibility to CRC Studies

Table 2. Results of *GSTP1* rs1695 Polymorphism and Risk of CRC in Iranian Population

Characteristics	A vs. G			AA vs. GG			AG vs. AA			AA + AG vs. GG			AA vs. AG + GG		
	OR	95% CI	P	OR	95% CI	p	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Total**	1.06	0.89-1.26	0.545	1.31	0.99-1.74	0.058	1.45	1.08-1.93	0.013	1.37	1.04-1.80	0.023	0.98	0.84-1.15	0.835
Female**	1.46	1.13-1.90	0.004	1.36	0.91-2.06	0.138	1.56	1.02-2.38	0.041	1.45	0.98-2.15	0.066	0.98	0.77-1.24	0.845
Male**	0.81	0.63-1.02	0.074	1.27	0.86-1.87	0.228	1.36	0.91-2.02	0.134	1.01	1.00-1.01	0.161	0.99	0.80-1.22	0.931
<50**	1.33	0.92-1.91	0.125	1.34	0.71-2.56	0.37	1.07	0.56-2.06	0.842	1.21	0.65-2.26	0.552	1.26	0.92-1.74	0.154
≥ 50**	1	0.82-1.22	0.989	1.34	0.98-1.83	0.07	1.63	1.18-2.26	0.003	1.45	1.07-1.97	0.016	0.91	0.76-1.09	0.317
Female vs. male	1.68	1.29-2.21	0.0001	1.34	0.89-2.03	0.167	1.29	0.84-1.98	0.244	1.32	0.89-1.97	0.174	1.1	0.86-1.41	0.457
< 50 vs. ≥ 50	1.04	0.77-1.40	0.799	0.71	0.43-1.18	0.185	0.53	0.32-0.89	0.016	0.63	0.38-1.02	0.062	0.78	0.59-1.02	0.074
Colon vs. rectum	1.17	0.84-1.62	0.36	1.02	0.62-1.68	0.937	1.03	0.61-1.729	0.926	1.02	0.63-1.66	0.928	0.99	0.74-1.32	0.935
Poor vs. moderate+well	0.97	0.62-1.51	0.891	0.9	0.47-1.74	0.761	1.46	0.72-2.97	0.296	1.08	0.57-2.05	0.818	0.68	0.45-1.02	0.061
I-II vs. III-IV	1.34	1.01-1.78	0.046	1.47	0.94-2.31	0.091	1.26	0.79-2.10	0.335	0.85	0.69-1.06	0.151	1.23	0.95-1.59	0.125

*, significant results; **, comparison of patients with controls; Abbreviations: TNM, Tumor, Node, Metastases; OR, odds ratio; CI, confidence interval

stress byproducts [14, 43]. This enzymatic inefficiency increases susceptibility to cellular damage and cancer, a vulnerability compounded by prolonged exposure to environmental carcinogens and age-related declines in cellular repair mechanisms, mitochondrial function, and immune surveillance [44, 45].

Females may experience accelerated aging 10 to 15 years earlier than men due to significant hormonal changes associated with menopause, which typically occurs around age 51 [46]. The decline in estrogen levels during menopause exacerbates oxidative stress and immune dysregulation, fostering a tumor-promoting environment [47, 48]. Estrogen plays a pivotal role in modulating antioxidant defenses and immune responses, highlighting its protective effects, which are diminished in postmenopausal women carrying the *GSTP1* rs1695 G allele. The combination of hormonal decline and the G allele's impaired detoxification capacity significantly increases CRC susceptibility in older females. These synergistic interactions emphasize the need to consider genetic predispositions and hormonal changes in CRC pathogenesis. Incorporating genetic and demographic factors, including hormonal status and genetic polymorphisms, into CRC risk assessments and prevention strategies is essential to address the vulnerabilities of high-risk subgroups, particularly postmenopausal women.

A prior study from Iran, with a sample size of 200, reported no significant association between the *GSTP1* rs1695 polymorphism and CRC risk in the overall analysis [35]. In contrast, the present study, with a substantially larger sample size and detailed subanalyses stratified by variables such as gender and age, demonstrated consistent overall results with the earlier study but highlighted significant associations in subgroup analyses. These findings underscore the importance of accounting for demographic variables in genetic association studies to better understand CRC risk in specific populations.

The accompanying meta-analysis, incorporating data from 30 studies alongside the current case-control study, provided a comprehensive overview of the *GSTP1* rs1695 polymorphism's role in CRC across diverse populations. While the overall meta-analysis, including stratifications by Asian, Caucasian, and mixed ethnic groups, did not reveal significant associations, the results align with the overall findings of this study. However, the absence of subgroup analyses based on critical demographic factors such as age and gender limits the depth of these findings. This underscores the need for future meta-analyses to incorporate detailed stratified analyses to uncover interactions between genetic and demographic factors influencing CRC risk.

Despite its strengths, this study has certain limitations. Data on patients' lifestyle factors, such as smoking, were unavailable, and there is a paucity of original studies from other regions of Asia, particularly the Middle East. Addressing these gaps in future research is essential for a more nuanced understanding of CRC risk in diverse populations.

In conclusion, this case-control study, the largest of its kind from Iran and the Middle East, suggests that

Table 3. Characteristics of the Reports of *GSTP1* rs1695 and Susceptibility to CRC, Including This Case-Control Study in the Current Meta-Analysis

No.	Author	Year	Origin	Ethnicity	Genotyping method	CRC (N)					Control (N)					HWE
						Genotypes			Alleles		Genotypes			Alleles		
						AA	AG	GG	A	G	AA	AG	GG	A	G	
1	Harries et al.	1997	UK	Caucasian	PCR	37	55	8	129	71	79	66	10	224	86	0.44
2	Harris et al.	1998	Australia	Caucasian	PCR	37	40	11	114	62	80	101	18	261	137	0.08
3	Katoh et al.	1999	Japan	Asian	PCR-RFLP	70	33	0	173	33	93	24	5	210	34	0.05
4	Welfare et al.	1999	UK	Caucasian	PCR	92	89	15	273	119	80	76	21	236	118	0.65
5	Loktionov et al.	2001	UK	Caucasian	PCR-RFLP	87	95	24	269	143	139	168	38	446	244	0.23
6	Sachse et al.	2002	UK	Caucasian	TaqMan assay	193	240	57	626	354	260	256	77	776	410	0.27
7	Kiss et al.	2004	Hungary	Caucasian	PCR-RFLP	200	212	88	612	388	214	212	74	640	360	0.07
8	Van der Logt et al.	2004	Netherland	Caucasian	PCR-RFLP	156	176	39	488	254	174	186	55	534	296	0.63
9	Ates et al.	2005	Turkey	Caucasian	PCR	73	81	27	227	135	90	74	40	254	154	0
10	Landi et al.	2005	Spain	Caucasian	Oligonucleotide micro-assay &APEX	184	162	32	530	226	148	131	37	427	205	0.34
11	Sun et al.	2005	Sweden	Caucasian	PCR-RFLP	59	51	15	169	81	127	101	27	355	155	0.31
12	Hang et al.	2006	China	Asian	PCR-RFLP	180	115	18	475	151	279	136	23	694	182	0.23
13	Martinez et al.	2006	Spain	Caucasian	PCR-RFLP	73	66	5	212	76	160	135	34	455	203	0.49
14	Skjelbred et al.	2007	Norway	Caucasian	PCR	51	50	7	152	64	119	140	40	378	220	0.91
15	Vlaykova et al.	2007	Bulgaria	Caucasian	PCR-RFLP	55	18	7	128	32	68	49	9	185	67	0.97
16	Kury et al.	2008	France	Caucasian	TaqMan assay	464	447	112	1375	671	541	462	118	1544	698	0.19
17	Epplein et al.	2009	USA	Mixed	TaqMan assay	113	59	15	285	89	188	110	41	486	192	0
18	Matakova et al.	2009	Slovak	Caucasian	PCR-RFLP	64	98	20	226	138	186	172	28	544	228	0.17
19	Hlavata et al.	2010	Czech	Caucasian	TaqMan assay	223	229	43	675	315	224	226	45	674	316	0.26
20	Yeh et al.	2010	China	Asian	PCR-RFLP	500	200	20	1200	240	511	196	25	1218	246	0.25
21	Koh et al.	2011	Singapore	Asian	TaqMan assay	343	122	15	808	152	771	345	51	1887	447	0.12
22	Wang et al.	2011	India	Asian	PCR-RFLP	141	132	29	414	190	160	107	24	427	155	0.31
23	Ebrahimkhani et al.	2012	Iran	Caucasian	PCR	54	39	6	147	51	53	42	5	148	52	0.36
24	Hezova et al.	2012	Czech	Caucasian	PCR-RFLP	103	74	20	280	114	93	100	25	286	150	0.81
25	Khabaz et al.	2012	Jordan	Caucasian	PCR-RFLP	43	45	2	131	49	24	31	1	79	33	0.01
26	Sameer et al.	2012	India	Asian	TaqMan assay	65	14	7	144	28	118	34	8	270	50	0.01
27	Wang et al.	2012	USA	Mixed	TaqMan assay	127	137	38	391	213	171	144	43	486	230	0.14
28	Gorukmez et al.	2016	Turkey	Caucasian	PCR-RFLP	76	28	7	180	42	61	58	3	180	64	0.01
29	Rodrigues-Fleming et al.	2018	Brazil	Mixed	PCR-RFLP	227	224	68	678	360	107	102	23	316	148	0.86
30	Nissar et al.	2019	Kashmiri	Asian	PCR-RFLP	121	26	13	268	52	148	42	10	338	62	0.01
31	This study	2025	Iran	Caucasian	TaqMan assay	548	382	108	1478	598	811	619	122	2241	863	0.78

Table 4. Continued

Ethnicity	AA vs. AG + GG				
	Association			Heterogeneity	
	ES	95% CI	P	I^2	p
Overall (31)	0.98	0.91-1.07	0.68	45	0.02
Asian (7)	0.94	0.77-1.14	50	55	0.03
Caucasian (21)	1.01	0.91-1.11	0.92	47	0.02
Mixed (3)	0.94	0.78-1.13	0.49	39	0.2
UK (4)	0.89	0.75-1.05	0.16	44	0.15
Iranian (2)	1.02	0.89-1.19	0.75	0	0.89

ES, effect size; OR, odds ratio; CI, confidence interval

the *GSTP1* rs1695 polymorphism contributes to CRC susceptibility in specific subgroups, particularly among Iranian women aged 50 or older. The potential of *GSTP1* as a biomarker for identifying high-risk groups, including postmenopausal women, underscores its relevance in CRC risk assessment. Future studies involving larger, ethnically diverse cohorts with detailed subgroup analyses are necessary to validate these findings and explore the mechanisms underlying the role of *GSTP1* in CRC development.

Author Contribution Statement

Monirosadat Haerian was responsible for sample recruitment, laboratory work, data analysis, and manuscript writing. Batoul Sadat Haerian contributed to data analysis and manuscript editing. Saadat Molanaei, Farid Kosari, Shahram Sabeti, Farahnaz Bidari-Zerehpoosh, and Ebrahim Abdolali contributed to sample access, diagnosis, and manuscript editing.

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Ethical Approval

This study was approved by the Ethics Committee

Table 4. Results of the Meta-Analysis on the *GSTP1* rs1695 Polymorphism and Its association with CRC Risk

Ethnicity	A vs. G					AA vs. GG					AG vs. AA					AA + AG vs. GG				
	Association			Heterogeneity		Association			Heterogeneity		Association			Heterogeneity		Association			Heterogeneity	
	ES	95% CI	P	I^2	p	ES	95% CI	P	I^2	p	ES	95% CI	P	I^2	p	ES	95% CI	P	I^2	p
Overall (31)	0.99	0.94-1.06	0.85	38	0.01	0.96	0.87-1.06	0.41	23	0.13	1.02	0.90-1.16	0.76	28	0.03	0.98	0.89-1.08	0.73	22	0.15
Asian (7)	0.96	0.83-1.11	0.57	46	0.02	0.95	0.72-1.25	0.72	9	0.36	1	0.75-1.33	0.99	0	0.44	0.98	0.74-1.28	0.86	0	0.47
Caucasian (21)	1.01	0.94-1.08	0.83	38	0.01	0.96	0.86-1.08	0.53	29	0.11	1.03	0.87-1.22	0.7	39	0.05	1.02	0.88-1.18	0.8	30	0.03
Mixed (3)	0.96	0.83-1.10	0.54	57	0.1	0.93	0.68-1.28	0.67	52	0.12	1.01	0.73-1.39	0.96	22	0.28	0.97	0.72-1.31	0.85	45	0.16
UK (4)	0.96	0.85-1.09	0.5	31	0.23	1.03	0.87-1.37	0.84	0	0.44	1.19	0.90-1.58	0.22	0	0.6	1.11	0.85-1.45	0.44	0	0.57
Iranian (2)	0.96	0.85-1.08	0.46	0	0.79	0.87	0.58-1.01	0.06	0	0.87	0.7	0.53-0.93	0.01	0	0.87	0.74	0.57-0.96	0.02	0	0.87

ES, effect size; OR, odds ratio; CI, confidence interval

of Shahid Beheshti University of Medical Sciences. The study has not been registered in any clinical trial or research registry.

Conflict of Interest

The authors declare no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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