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Research Article

CYP1A1 and *GSTM1* genes associated with the risk of developing colorectal cancer: a case-control study in the Lima region of Peru

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Abstract

The presence of *CYP1A1* allelic variants and deletion of the glutathione S-transferase *GSTM1* gene, and their imbalance, have been suggested as risk factors for inducing colorectal cancer (CRCa). The objective was to identify *CYP1A1* and *GSTM1* and evaluate the association with the risk of developing colorectal cancer in a sample of cases and controls from Lima, Peru. This was a case-control study of *CYP1A1* and *GSTM1* genes in 50 samples from patients diagnosed with colorectal cancer and 50 samples from controls without cancer, using the PCR-based restriction fragment length polymorphism method. A significant risk of developing CRCa was found in the following groups: *GSTM1*0* carriers with no history of smoking or family history of cancer (OR = 3.56, 95% CI 1.43–8.88, p = 0.0060); *GSTM1*0* with family history of cancer without smoking (OR = 2.81, 95% CI 0.35–22.49, p = 0.3280); *GSTM1**0 exacerbated by smoking (OR = 1.41, 95% CI 0.11–17.11, p = 0.7880); *CYP1A1*2A/*2A* carriers with family history and smoking (OR = 1.50, 95% CI 0.13–16.54, p = 0.7410). An association of wild genotypes exacerbated by non-genetic factors with risk of developing CRCa was also found: *CYP1A1**1A/*1A with family history of cancer but no history of smoking (OR = 2.94, 95% CI 0.11–35.80, p = 0.6380); *GSTM1* (+) with history of smoking but no family history of cancer (OR = 5.63, 95% CI 0.46–68.46, p = 0.1750); *GSTM1* (+) associated with family history and smoking (OR = 9.86, 95% CI 1.77–54.89, p = 0.0090). According to univariate statistical analysis, carriers of *CYP1A1**2A and *GSTM1**0 without association with family history of cancer and smoking would not

be related to the risk of CRCa. An association was established between *GSTM1*0* and *CYPA1*2A/*2A* with colorectal cancer exacerbated by family history and smoking. The risk is higher with wild-type genotypes of *CYP1A1**1A/*1A and *GSTM1* (+) induced by family history and smoking, respectively.

Keywords

CYP1A1, *GSTM1*, colorectal cancer, smoking, family history

Introduction

Growths of the inner lining of the colon or rectum are referred to as adenomatous polyps (adenomas), sessile serrated polyps (SSPs), and traditional serrated adenomas (TSAs), which, over time, can develop into colorectal cancer (CRCa). CRCa ranks third among the most common neoplasias in men and second in women. By 2022, it was projected that 1,918,030 new cases of cancer and 609,360 cancer-related deaths would occur in the United States (Siegel et al. 2022; Li et al. 2023; Zhang et al. 2023). With an annual incidence comprising 10% of all neoplasias and a poor prognosis, CRCa is considered the second leading cause of cancer mortality (Siegel et al. 2020; Biller and Schrag 2021; Li et al. 2023). In Peru, CRCa ranks as the third most frequent neoplasia, with 384 new cases registered in the first quarter of 2024, affecting 171 men and 213 women. Lima is the department with the highest rates of detection and mortality from colorectal cancer (Ministry of Health 2024). Due to its high morbidity and mortality, significant burden on healthcare systems, and the high cost of treatment, this type of cancer represents a serious global public health problem (Qiu et al. 2021; Kocarnik et al. 2022; Li et al. 2023). Multiple risk factors have been associated with the development of colorectal cancer, including smoking, chronic alcohol consumption, intake of procarcinogenic substances (Poynter et al. 2009; Storm et al. 2010; Jin et al. 2011; Sninsky et al. 2022), family history, physical inactivity, and obesity (Sninsky et al. 2022). Genetic risk factors include *CYP1A1* genes, which activate procarcinogenic substances, and null *GSTM1* genes (Lee et al. 2006; Jin et al. 2011; Alvarado et al. 2021a; Alvarado et al. 2025). Smoking and alcohol consumption are high-risk factors for traditional serrated adenomas (TSAs) (Scherübl 2021; Sninsky et al. 2022), likely due to the presence of polycyclic aromatic hydrocarbons in cigarette smoke (Naif et al. 2018), whose mechanism of action involves DNA methylation (Zhou et al. 2023).

The *CYP1A1* gene is mapped to the long arm (q) of chromosome 15, region 24.1 (15q24.1). The *CYP1A1*1A* allele constitutes the homozygous wild-type genotype *CYP1A1**1A/**1A* (T/T, W1/W1), which lacks the Msp I site (Rahal et al. 2013; Alvarado et al. 2021a; Alvarado et al. 2025). This gene is expressed in the esophagus, stomach, small intestine, colon, lungs, prostate, and breast, and is therefore potentially involved in the development of neoplasias in these organs (Masson et al. 2005; Barbosa et al. 2016). Two single nucleotide polymorphisms (SNPs) are well documented for their association with cancer. One is *CYP1A1*2A* (also referred to as *CYP1A1* Msp I, *CYP1A1* m1, or *CYP1A1*2B*; rs4646903, T>C), which can result in the heterozygous genotype *CYP1A1**1A/**2A* (T/C, W1/m1) or the homozygous mutant genotype *CYP1A1**2A/**2A* (C/C, m1/m1), both of which include the Msp I site (Barbosa et al. 2016; Rosero et al. 2016). The second SNP is *CYP1A1*2C* 462Ile>Val (*CYP1A1* m2; rs1048943), which results from the substitution of adenine (A) with guanine (G) at nucleotide 2455 (2455A>G) in the heme-binding region of exon 7, causing an amino acid change from isoleucine (Ile) to valine (Val) at codon 462 (462Ile>Val) (Sivaraman et al. 1994; Liu et al. 2013; Roszak et al. 2014; Sánchez-Siles et al. 2020). The *GSTM1* gene (glutathione S-transferase mu-1; GTH4), located on the short arm (p) of chromosome 1, region 13.3 (1p13.3), is expressed in the gastrointestinal tract, where it encodes GSTM1 (GST mu-1), GSTP1 (GST pi), and GSTT1 (GST theta) proteins (Lee et al. 2006; Rosero et al. 2016; García-Martínez et al. 2017). This gene has a wild-type allele, *GSTM1* (+), and a null allele, *GSTM1*0* (– or del), which results from the deletion of an approximately 18 kb segment. Individuals with a homozygous deletion of both alleles (*GSTM1 *0/0* or del/del) lack gene expression (Rosero et al. 2016; Satinder et al. 2017; Sánchez-Siles et al. 2020). Fig. 1A shows the location of the *CYP1A1* gene and its protein-coding sequence. Fig. 1B illustrates the deletion of the *GSTM1* gene.

The allelic variants *CYP1A1*2A* (Msp I) and *CYP1A1*2* 462Ile>Val encode highly active CYP1A1 enzymes involved in the oxidation of estrogen into 2-hydroxyestrogen and in the biotransformation of procarcinogens (benzopyrene), arylamines, N-nitrosamines (from tobacco), and dioxins into highly reactive metabolites that bind to a DNA segment, generating adducts and the development of neoplasias (Murtaugh et al. 2005; Zisman et al. 2006; Wang et al. 2008; Alvarado et al. 2021a; Alvarado et al. 2025). While glutathione S-transferase (GST) isoenzymes participate in phase II conjugation metabolism by incorporating glutathione into various xenobiotic agents (drugs, oxidative stress products, environmental toxins, and procarcinogens) to convert them into hydrophilic molecules and eliminate

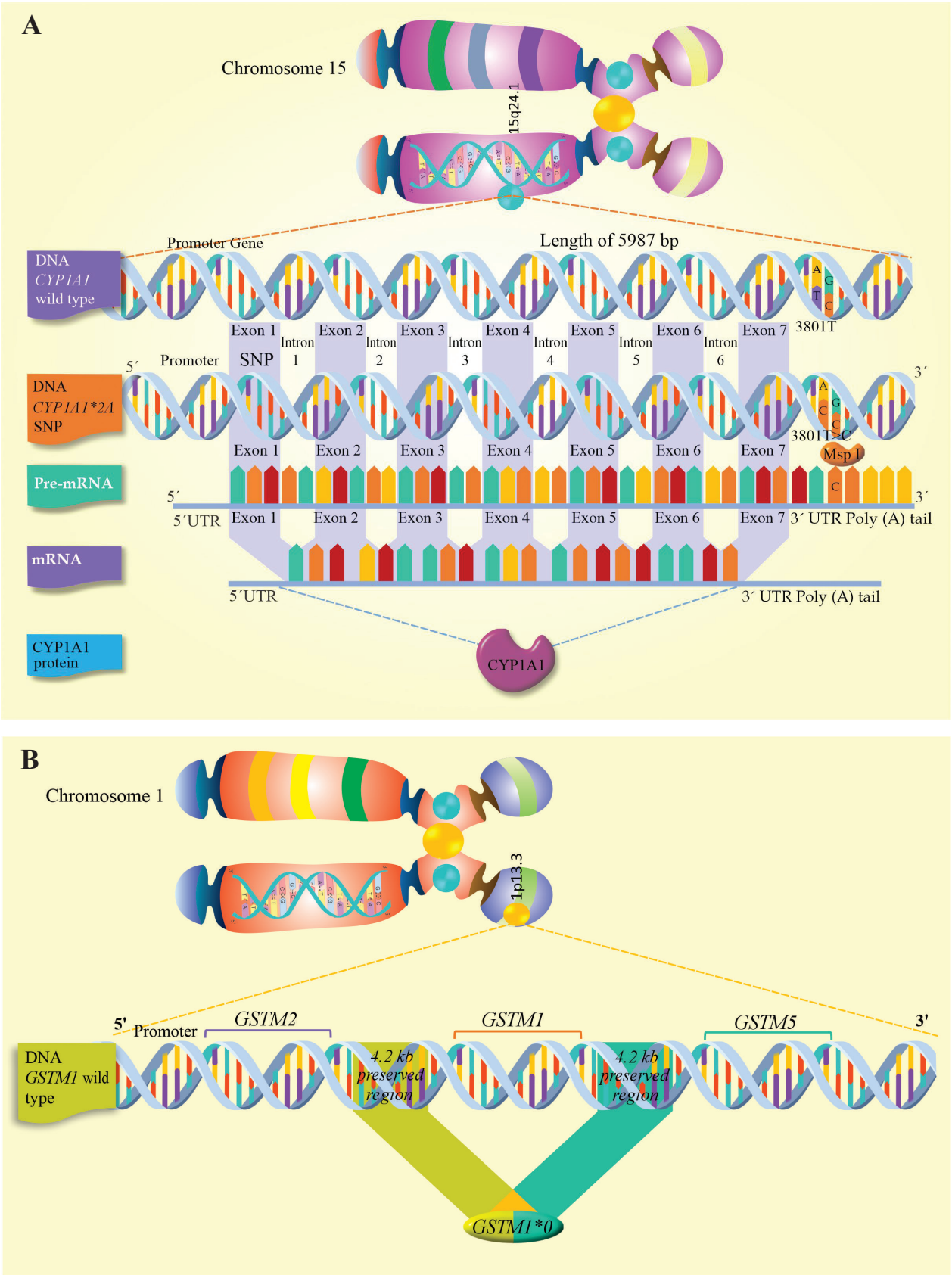

Figure 1. A. Locations of the *CYP1A1* and *GSTM1* genes, SNP *CYP1A1*2A*, and the *GSTM1*0* deletion. **B.** *GSTM1*0* is generated when the highly conserved 4.2 kb regions at the 5' and 3' ends of the *GSTM1* gene undergo unequal recombination; that is, two repeated segments join together, causing the loss of an approximate 18 kb segment.

them through the bile, in this sense, in *GSTM1*0* carriers the xenobiotic detoxifying protein GSTM1 is not expressed, exposing them to cytogenetic damage and genomic instability that predisposes them to greater susceptibility to developing cancer (Acar et al. 2006; Rosero et al. 2016; Satinder et al. 2017).

After reviewing the PubMed-NCBI database on research on genes and allelic variants of *CYP1A1* and deletions of the *GSTM1* gene in patients with colorectal cancer in Peru, it is evident that they have not yet been examined in these populations. In this sense, these studies are justified for three reasons: First, to evaluate whether *CYP1A1* and *GSTM1* gene carriers are associated with colorectal cancer in patients residing in Lima of tricontinental descent; second, to evaluate whether *CYP1A1/GSTM1* genes associated with a family history of any type of cancer and smoking are susceptibility factors for developing colorectal cancer; Third, to generate scientific evidence of the association between genotype and colorectal cancer and to propose the implementation of precision medicine in the country to reduce adverse reactions and ensure the effectiveness of cancer treatment. Understanding whether genetic and nongenetic predictive factors are associated with colorectal cancer will allow for prevention or early detection in these high-risk groups to reduce the incidence of this cancer. Therefore, the objective was to identify *CYP1A1* and *GSTM1* and evaluate the association with the risk of developing colorectal cancer in a sample of cases and controls from Lima, Peru.

Materials and methods

Design, study type, and study population

Observational, analytical case-control study, with prospective recruitment between September 2022 and December 2023. Patients diagnosed with colorectal cancer (CRCa) from the Central Military Hospital and the general Peruvian control population (PC) were invited to participate in the study. To this end, they were previously informed about the objectives and importance of the research, and then volunteers were selected using non-probability and convenience sampling. The sample size was 100 volunteer participants: 50 patients (female, n = 19; male, n = 31) and 50 controls (female, n = 19; male, n = 31).

Inclusion and exclusion criteria

Patients with a diagnosis of colorectal cancer (CRCa) confirmed by histology indicating sessile serrated polyp (SSP) and traditional serrated adenoma (TSA), without other chronic disease, of both sexes, older than 18 years, and without a family relationship were included in the present study. The Peruvian general control population was included after a clinical examination and had to be in good health, without any family relationship with the patients, and after giving their written consent.

Family members of patients and controls, patients and control subjects who did not sign the informed consent form, and those who did not meet the inclusion criteria were excluded from the study.

Ethical considerations

The study was carried out in strict compliance with national ethical standards; procedures suggested in the 1964 Declaration of Helsinki with the current revision; Good Clinical Practice guidelines; and strict ethical procedures recommended by the Research Ethics Committee of the Central Military Hospital (Report No. 25-CIE-12/09/2022). Everyone was assigned a code to ensure anonymity and confidentiality. All participants (volunteers and patients) signed a written informed consent form to participate in the study. The control volunteers remained in contact with the research oncologists to determine whether they might develop CRC during the study period.

DNA isolation and genotyping

Genomic DNA (gDNA) was isolated from blood samples using the innuPRE DNA Master Kit™ (Analytik Jena™) and subsequently quantified by spectrophotometry using Denovix equipment (model DS-11, FX, Spectrophotometer Series™, USA). Samples with absorbance ratios of 260/280 nm and 260/230 nm equal to or greater than 1.7 were considered suitable for the study. Restriction fragment length polymorphism (RFLP) based on polymerase chain reaction (PCR) was used to genotype the *CYP1A1*2A* (rs4646903 T>C) polymorphism, using the following primer sequences: forward primer 5' CAGTGAAGAGTGTGTAGCCGCT-3' and reverse primer 5' TAGGAGTCTTGT TCATGCCT-3'. The deletion of the GSTM1 gene was determined using the following primers, 5'GAACTCCCTGAAAGCTAAAGC-3' and 5'GTTGGGCTCAAAATACGTGG-3'.

After an initial denaturation at 94 °C for 3 min, samples were subjected to 30 cycles for 30 s at 94 °C, 30 s at 55 °C, and 1 min at 72 °C, followed by final extension at 72 °C for 5 min. A fraction of the PCR product was subjected to 2% agarose gel electrophoresis, and the presence of amplicons was identified by staining with GelRed (Biotium®) and ultraviolet transilluminator. For the *GSTM1* gene, the null genotype (*GSTM1*0*) corresponds to a homozygous deletion of the gene, as seen by the absence of a 215-bp amplification fragment; *GSTM1*(+) individuals present the wild-type allele in either homozygous or heterozygous form, as determined by the presence of the aforementioned fragment (215 bp). As an internal amplification control, the amplicon obtained with the primers for *CYP1A1*2A* was used.

To obtain *CYP1A1*2A* genotypes, the PCR product was digested with the MspI enzyme (FastDigest® MspI, Ref: FD0544; Thermo Fisher Scientific Baltics UAB) at 37 °C for 15 minutes. The digestion system contained 8 μL of PCR products, 1 μL of 10× FastDigest Green Buffer, and 1 μL

of MspI. The digested products were separated by 2% agarose gel electrophoresis and then visualized with GelRed (Biotium®) in an ultraviolet transilluminator. The presence of the wild genotype *1A/1A* (T/T) is observed by a single band of 340 bp, the genotype *1A/2A* (T/C) was identified by three bands of 340, 200, and 140 bp, and the genotype *2A/2A* (C/C) was identified by two bands of 200 and 140 bp (Lee et al. 2006; Roco et al. 2012; Roco et al. 2019).

Statistical analyses

The expected genotype frequencies for *CYP1A1* and *GSTM1* were determined by direct counting from the allele frequencies. Associations between genotype carriers, smokers, family history, and the risk of colorectal adenomas were assessed using odds ratios (ORs) and 95% CIs using Woolf's method. To determine whether the distribution of the genotypes of the control population was in Hardy-Weinberg equilibrium (HWE), the chi-square goodness-of-fit test (χ^2) was used, considering one degree of freedom and a p-value <0.05. χ^2 values greater than 3.88 in the comparison indicated rejection of the null hypothesis; therefore, the observed frequencies differed significantly from those expected (Alvarado et al. 2019; Roco et al. 2019; Alvarado et al. 2021b). All statistical analyses were performed by age using Stata software, version 12.0 (StataCorp LP, Texas, USA).

Results

As part of routine clinical practice and diagnosis of the disease, carcinoembryonic antigen (CEA) was requested as a tumor marker, and among 16 patients who were candidates for the use of monoclonal antibodies, genetic analysis of the KRAS gene was indicated. The mutated KRAS gene was found in five patients; therefore, the use of monoclonal immunotherapy was not possible in them. Additionally, data on chronic tobacco use and family history of any type of cancer were requested from controls (general Peruvian population) and patients with colorectal cancer. It is observed that there is a statistically significant difference with respect to smoking (p-value 0.1107). Fisher's exact test was applied to analyze whether the qualitative variable of family history of any type of cancer is associated with colorectal cancer (small n = 50); the observed result is statistically significant (p-value 0.016), indicating a possible association in the participants of the present study (Table 1).

Table 2 shows the allele and genotype frequencies obtained from patients with colorectal cancer (CRCa) and the general Peruvian control population (PC). Using the chi-square goodness-of-fit test (χ^2), it is observed that the comparison values are less than 3.84 with a degree of freedom and confidence level of 95%, demonstrating that there is no significant statistical difference, given that the observed and expected frequencies are equal; therefore, the distribution of the genotypes is in Hardy-Weinberg equilibrium (HWE).

Table 1. General and clinical-diagnostic characteristics of the study groups.

Characteristics	PC (n = 50)	CRCa (n = 50)	p-value
Age			
Mean ± SD	44.20 ± 14.44	68.46 ± 12.99	1.47×10^{-14}
Range in years	22–72	36–89	
Smoking			
Yes (≥ 20 pack/years)	5	11	0.1107
No (<20 pack/years)	45	39	
Cancer family history (any type)			
Yes	4	12	0.0160*
No	46	38	
Tumor marker diagnostic test			
CEA	UD	49	
KRAS gene mutation study			
Mutated	UD	5	
Not mutated	UD	11	
Undetermined	–	34	

CP, Peruvian general population control; CRCa, colorectal cancer patients; CEA, carcinoembryonic antigen; UD, undetermined; p<0.05, statistically significant; *Fischer's exact test.

Table 2. Frequency of the *CYP1A1* allele and genotype in patients with colorectal cancer and the Peruvian general population control.

Genotype	CRca n (%)	χ^2	PC n (%)	χ^2
*CYP1A1*1A/*1A* (T/T)	7 (14)	0.042	4 (8)	0.738
*CYP1A1*1A/*2A* (T/C)	22 (44)	0.047	27 (54)	0.794
*CYP1A1*2A/*2A* (C/C)	21 (42)	0.013	19 (38)	0.213
Total	50 (100)	0.102	50 (100)	1.745
Allele	CRca (%)		PC (%)	
*CYP1A1*1A*	36		35	
*CYP1A1*2A*	64		65	
Total	100		100	

CRCa, colorectal cancer patients; PC, Peruvian general population control; n: sample number; χ^2, chi square test.

Table 3. Frequency of the *GSTM1* genotype in patients with colorectal cancer and Peruvian general population control.

Genotype	CRca n (%)	PC n (%)
GSTM1 (+)	22 (44)	27 (54)
*GSTM1*0*	28 (56)	23 (46)
Total	50 (100)	50 (100)

In samples from patients with colorectal cancer and the general Peruvian control population, *GSTM1*0* genes were observed with a frequency of 56% and 46%, respectively, as shown in Table 3.

In the general Peruvian population, the frequency of *CYP1A1*2A* (**1A/*2A* and **2A/*2A*) was found to be 65%. Regarding its tricontinental ancestry, it is observed that this gene is more frequent in the Asian population and less frequent in the European and African populations. While the *GSTM1*0* null genotype is more common in Peruvian patients and the population, it is also more common in Europeans, Africans, and Asians, exceeding 50% (Table 4).

Table 4. Frequency of *CYP1A1*2* alleles and *GSTM1*0* null genotypes in the general population and Peruvian patients with colorectal cancer compared to their tricontinental ancestry.

Population	Frequency (%)		Reference
	***CYP1A1*2A* dbSNP: rs4646903**	***GSTM1*0***	
Peruvian patients with CRCa (n = 50)	64	56	Current study
Peruvian population control (n = 50)	65	46	Current study
European population	9–33*	50**	(Masson et al. 2005*; Varela-Lema et al. 2008 **)
African population	18.81*	56**	(Medjani et al. 2020*; Lee et al. 2008**)
East Asian population	47.1*; 34–73**	56*	(Lee et al. 2008*; Masson et al. 2005**)

dbSNP, database number for single nucleotide polymorphisms (SNP); CP, control of the Peruvian population; CRCa, colorectal cancer patients

Table 5. Univariate logistic regression analysis of risk of developing colorectal cancer in relation to genotypes, family history of cancer, and smoking habit.

Genotype (50 controls vs 50 cases)	OR	95% CI	p-value
*CYP1A1*2A*	0.46	0.12–1.68	0.2440
*CYP1A1*1A/*1A*	1.00	–	Ref.
*CYP1A1*1A/*2A*	0.46	0.12–1.79	0.2680
*CYP1A1*2A/*2A*	0.46	0.11–1.79	0.5109
GSTM1			
+/+	1.00	–	Ref.
-/-	1.88	0.87–4.06	0.1070
Smoking			
No	1.00	–	Ref.
Yes	2.93	0.94–9.13	0.063
Cancer family history			
No	1.00	–	Ref.
Yes	4.18	1.25–13.97	0.020

OR, odds ratio; 95% CI, 95% confidence interval; Ref., reference; $p < 0.05$, statistically significant.

To elucidate the possible association between genotype carriers and the risk of developing colorectal cancer (CRCa) among cases and controls, odds ratios (OR) with 95% confidence intervals (95% CI) were calculated, as shown in Table 5. The heterozygous *CYP1A1**1A/*2A genotype (OR = 0.46; 95% CI: 0.12–1.79; p = 0.2680) and the homozygous *CYP1A1**2A/*2A genotype (OR = 0.46; 95% CI: 0.11–1.79; p = 0.5109) were not significantly associated with an increased risk of CRCa. Similarly, the risk associated with the *GSTM1*0* null genotype and smoking was low. In contrast, a family history of various cancers showed a moderate risk of developing CRCa.

Table 6 shows the statistical results of the combination of genotypes, family history of cancer, and smoking as risk factors for developing CRCa. An increased risk of developing CRCa is observed in patients carrying *GSTM1* (+) in association with a family history of cancer and smoking. There may also be a moderate risk of inducing CRCa in the following associations: *GSTM1* (+) with no family history of cancer but chronic smokers; *GSTM1*0* with no family history of cancer or smoking; While patients carrying *CYP1A1*1A/*1A* with a family history of cancer and no smoking have a small risk of developing CRCa, a similar risk is present in carriers of *GSTM1*0*. The other associations are insignificant.

Discussion

This research has studied the single nucleotide polymorphism of *CYP1A1*2A*, the deletion of *GSTM1*, and non-genetic factors such as smoking and family history involved in the development of colorectal cancer (CRCa). The smoking category included all patients and members of the general Peruvian population who smoked more than 1.5 packs of cigarettes per month (20 packs/year), considering smoking as a chronic and addictive nicotine disease that begins before age 18 in 80% of cases (Álvarez Mavárez et al. 2023). Regarding carcinoembryonic antigen (CEA), an oncofetal glycoprotein frequently elevated in CRCa (Hermida Lazcano et al. 2016), patients with values > 5 ng/mL show poor prognosis regardless of tumor stage (Cerezo Ruiz et al. 2014). In this study, mutations in the KRAS gene were found in five patients who were consequently not prescribed monoclonal antibody therapy. Previous studies report KRAS mutations in 30–50% of CRCa patients, correlating with resistance to monoclonal antibody therapy (Roa et al. 2013). Tables 2, 3 describe the frequencies of *CYP1A1* and *GSTM1* in patients with CRCa and the general Peruvian control population, respectively, while Table 4 compares these gene frequencies with European, African, and Asian populations, reflecting the tricontinental ancestry of Peruvians (Alvarado et al. 2023). The CYP1A1*2A allele is present in 65% of the Peruvian population, differing by 8–31% from Asian populations (32–55% *1A/*2A and 2–18% *2A/*2A), and is more frequent than in European populations (9–28% *1A/*2A and 0–5% *2A/*2A) (Masson et al. 2005) and African populations (46.19%) (Medjani et al. 2020). Regarding *GSTM1*0*, 46% prevalence was observed in this study, similar to Europeans (50%) (Varela-Lema et al. 2008), while African and Asian populations have approximately 10% higher frequencies (Lee et al. 2008). These differences are attributed to natural evolution, internal migration, and mixing among populations from the Coast, Andes, and Jungle regions of Peru (Alvarado et al. 2021b; Alvarado et al. 2023). To determine whether the *CYP1A1* and *GSTM1* genes, family history of cancer, and smoking are associated with the risk of developing CRCa, statistical analysis was performed using odds ratios (OR) and 95% confidence intervals (CI) via the Woolf method. In this study, it was found that *CYP1A1*1A/*2A* and *CYP1A1*2A/*2A* genotypes alone are not significantly associated with CRCa

Table 6. Statistical association of the risk of developing colorectal cancer in relation to smoking, family history of cancer, and genotypes.

Variables	CRCa	PC	Total	OR	95% CI	*p-value*
***CYP1A1*2A* (rs4646903)**	3	3	6	1.0	–	Ref.
*CYP1A1*1A/*1A*+ CFH (-) + SH (-)						
*CYP1A1*1A/*1A*+ CFH (-) + SH (+)	1	0	1	–	–	1.000*
*CYP1A1*1A/*1A*+ CFH (+) + SH (-)	2	1	3	2.94	0.11–35.80	0.638
*CYP1A*1A/*1A*+ CFH (+) + SH (+)	1	0	1	–	–	1.000*
*CYP1A1*1A/*2A*+ CFH (-) + SH (-)	16	26	42	0.62	0.11–3.42	0.579
*CYP1A1*1A/*2A*+ CFH (-) + SH (+)	0	1	1	–	–	1.000*
*CYP1A1*1A/*2A*+ CFH (+) + SH (-)	2	0	2	–	–	0.464
*CYP1A1*1A/*2A*+ CFH (+) + SH (-)	4	0	4	–	–	0.200*
*CYPA1*2A/*2A*+ CFH (-) + SH (-)	16	21	37	0.76	0.13–4.28	0.758
*CYPA1*2A/*2A*+ CFH (-) + SH (+)	2	2	4	1.00	0.08–12.55	1.000
*CYPA1*2A/*2A*+ CFH (+) + SH (-)	0	1	1	–	–	1.000*
*CYPA1*2A/*2A*+ CFH (+) + SH (+)	3	2	5	1.50	0.13–16.54	0.741
GSTM1						
GSTM1 (+) + CFH (-) + SH (-)	11	31	42	1.0	–	Ref.
GSTM1 (+) + CFH (-) + SH (+)	2	1	3	5.63	0.46–68.46	0.1750
GSTM1 (+) + CFH (+) + SH (-)	2	0	2	–	–	0.0820*
GSTM1 (+) + CFH (+) + SH (+)	7	2	9	9.86	1.77–54.83	0.0090
*GSTM1*0* + CFH (-) + SH (-)	24	19	43	3.56	1.43–8.88	0.0060
*GSTM1*0* + CFH (-) + SH (+)	1	2	3	1.41	0.11–17.11	0.7880
*GSTM1*0* + CFH (+) + SH (-)	2	2	4	2.81	0.35–22.49	0.3280
*GSTM1*0* + CFH (+) + SH (+)	1	0	1	–	–	0.2790*

CFH: cancer family history; SH: smoking; * Fischer's exact test; (+) present; (-) absent/null; OR, odds ratio adjusted by age

(OR = 0.46, 95% CI: 0.12–1.79, p = 0.2680; OR = 0.46, 95% CI: 0.11–1.79, p = 0.5109, respectively). These findings are similar to those observed by Hamachi et al. (2013) in a case-control study, which indicated no significant association between *CYP1A1*2A* (OR = 0.89, 95% CI: 0.63–1.25) and colorectal adenomas. In a recent study by Patil et al. (2024), *CYP1A1*2A* was observed to have an OR of 1.72 (95% CI: 0.89–3.31, p = 0.10) in patients with CRCa.

Regarding *GSTM1*0* carriers, a greater susceptibility to the risk of developing CRCa was observed (OR = 1.88, 95% CI: 0.87–4.06, p = 0.1070). This finding suggests that gene deletion, which results in the absence of GST enzyme expression, could influence the degree and type of CRCa. In the smoking group, a similar risk of susceptibility to CRCa was found (OR = 2.93, 95% CI: 0.94–9.13, p = 0.063). A statistical association was also established for a higher risk of developing CRCa in individuals with a family history of different types of cancer (OR = 4.18, 95% CI: 1.25–13.97, p < 0.001). This non-genetic factor is associated with the induction of CRCa in various populations, and its incidence could be reduced by raising public awareness to reduce or minimize tobacco use. Smoking has been associated with various types of cancer for many years, including in the study by Cleary et al. (2010), who found a significant association between chronic smokers of more than 27 years and the risk of CRCa (OR = 1.25, 95% CI: 1.02–1.53). In another study conducted by Nisa et al. (2010), an association was found between smoking (≥400 cigarettes/year) and rectal cancer (OR = 1.60, 95% CI: 1.04–2.45).

In other research and populations, it has been reported that *GSTM1*0* carriers have also been associated with increased susceptibility to CRCa. For example, Klusek et al. (2018) reported an association between the *GSTM1* genotype (-/-) (OR = 1.1, 95% CI: 0.7–1.7, p = 0.80) and lymph node metastasis due to CRCa. Meta-analyses have likewise demonstrated associations, such as that by Li et al. (2015), who described a significant association of *GSTM1*0* (OR = 1.05, 95% CI: 1.02–1.07) with CRCa risk in Asians, particularly Chinese populations. Similarly, Liang Song et al. (2020) reported that the *GSTM1* (-/-) genotype is associated with a higher risk of CRCa in Caucasian (OR = 1.14, 95% CI: 1.05–1.23) and Asian populations (OR = 1.19, 95% CI: 1.08–1.32). Recently, Szuman et al. (2024) confirmed the association of the deleted *GSTM1*0* gene with an increased risk of CRCa in Czech and Bulgarian populations (OR = 1.30 and OR = 2.32, respectively). In other studies, the *CYP1A1* and *GSTM1* genes have also been associated with CRCa. For example, research by Darazy et al. (2011) indicated an association between *GSTM1* (-/-) and CRCa (OR = 3.8, 95% CI: 1.7–8.5), and *CYP1A1*2A/*2A* is related to gastric cancer in Lebanese patients. Saeed et al. (2013) reported a statistically significant association between Saudi patients with colorectal cancer and *CYP1A*1A/*2A* (OR = 3.65, 95% CI: 1.39–9.57). Likewise, Khan et al. (2022) demonstrated that *GSTM1*0* is significantly associated (OR = 3.131, 95% CI 1.451–6.758, p = 0.004) with the risk of CRCa in Pakistani residents.

A combined statistical analysis was also performed between *CYP1A1/GSTM1* genotypes and non-genetic factors in relation to the risk of developing CRCa (Table 6). Carriers of *GSTM1*0* were found to be 3.56 times more likely to develop CRCa (OR = 3.56, 95% CI: 1.43–8.88, p = 0.0060), even without a family history of cancer or chronic smoking. This significantly elevated risk should be consid-

ered in understanding the genesis of CRCa. Among patients carrying *GSTM1*0* with a family history of cancer but who were not chronic smokers, there is an association (OR = 2.81, 95% CI 0.35–22.49, p = 0.3280); in the other group of *GSTM1*0* exacerbated by smoking, an association was observed (OR = 1.41, 95% CI 0.11–17.11, p = 0.7880). Therefore, both groups have a higher likelihood of developing CRCa. Furthermore, *CYP1A1*2A/*2A* carriers with a family history of smoking have a 1.5-fold increased likelihood of developing CRCa (OR = 1.50, 95% CI: 0.13–16.54, p = 0.741). Notably, patients carrying the wild-type *CYP1A1*1A/*1A* genotypes, aggravated by family history of cancer but without smoking history, have a 2.94-fold increased risk (OR = 2.94, 95% CI: 0.11–35.80, p = 0.638) of developing CRCa. In addition, *GSTM1*(+) carriers with a history of smoking but no family history of cancer show a 5.63-fold increased likelihood of developing CRCa (OR = 5.63, 95% CI: 0.46–68.46, p = 0.1750).

In the other group with *GSTM1* (+) associated with the two non-genetic factors (family history and smoking), they would have greater susceptibility to the risk of developing CRCa (OR = 9.86, 95% CI: 1.77–54.89, p = 0.0090) than those who do not have risk factors. A previous study by Yoshida et al. (2007) showed that the *CYP1A1*2A* genotype is significantly associated (OR = 3.06, 95% CI 1.11–8.40; p = 0.030) with the risk of CRCa without smoking exposure. Later, Cleary et al. (2010) demonstrated an association of *GSTM1* (c.597G>C; OR = 1.99, 95% CI 1.21–3.25) with the risk of CRCa, and *CYP1A1*2A/*2A* was associated with lower risk (OR = 0.47, 95% CI 0.23–0.94). In a meta-analysis conducted by Du et al. (2018), a potential interaction between smoking and *GSTM1*0* (OR = 1.382, 95% CI: 1.009–1.894, p = 0.044) with the risk of suffering from esophageal cancer was evidenced. In another study, Sindi et al. (2021) found an association between *GSTM1* (OR = 3.7, p < 0.0001) and a significant risk of CRCa in Saudi nonsmokers; *CYP1A1* may also predispose to the risk of CRCa.

This study has some limitations. The first is the small case-control sample (n = 50); this small number of patients can generate false associations or non-associations in the statistical analysis. Another important bias is the very small sample size with respect to smoking and family history of cancer, resulting in variable estimates of associations with colorectal cancer risk. Notwithstanding the above, these findings will form part of the scientific evidence for oncologists to consider these genes as possible predictors of CRCa susceptibility and promote 4P medicine. Additionally, it serves as a scientific basis for researchers to consider conducting various studies.

We recommend conducting observational studies, randomized clinical trials (RCTs), and multicenter studies on these genes with larger sample sizes and better representation of relevant variables. With more robust scientific evidence, these genes may serve as potential biomarkers for the personalized diagnosis and treatment of CRCa. This would likely lead to improved clinical outcomes, reduced adverse reactions from antineoplastic drugs, and greater diagnostic and therapeutic accuracy.

Conclusion

In the univariate statistical analysis, we found that carriers of *CYP1A1*2A* and *GSTM1*0* without association with family history of cancer and smoking would not be related to a higher risk of CRCa. However, an association was established between *GSTM1*0* and *CYPA1*2A/*2A* with colorectal cancer exacerbated by family history and smoking; the risk being higher with wild genotypes of *CYP1A1*1A/*1A* and *GSTM1* (+) induced by family history and smoking, respectively.

On the other hand, wild-type genotypes, allelic variants, and the *GSTM1*0* deletion are present and prevalent in both patients and the general Peruvian population. These initial findings may be useful for a better understanding of the etiology of colorectal cancer.

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Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that experiments on humans or human tissues were performed for the present study.

Informed consent from the humans, donors or donors' representatives: Research Ethics Committee of the Central Military Hospital (Report No. 25-CIE-12/09/2022).

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Data availability

All of the data that support the findings of this study are available in the main text.

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