RESEARCH ARTICLE

Editorial Process: Submission:03/05/2024 Acceptance:02/06/2025

Cytochrome *P450 17 (CYP17), CYP2C19*2, CYP2C19*3* Gene Polymorphisms and Gastrointestinal Cancer Risk in Rural Maharashtra: A Hospital based Case-Control Study

Kailas D. Datkhile[1]*, Ashwini L. More[1], Madhavi N. Patil[1], Rashmi A. Gudur[2], Anand K. Gudur[2]

Abstract

Background: Gastrointestinal cancer (GI) is one of the most common cancer worldwide rapidly increasing in India too. Cytochrome P450 (CYP) family comprise a group of phase I metabolizing enzymes which are important in xenobiotics and carcinogen metabolism. Several studies revealed the association of metabolic genes with risk of cancers, but the results were ambiguous to support the evidences in case of GI cancer risk. These differences in earlier studies directed us to review the association of polymorphisms of metabolic genes including *CYP17* and *CYP2C19* (*CYP2C19*2, CYP2C19*3*) with GI cancer susceptibility in rural population of Maharashtra. **Methods:** Genetic polymorphism of *CYP17* and *CYP2C19* (*CYP2C19*2, CYP2C19*3*) genes among two hundred histologically confirmed gastrointestinal cancer cases and equal number of age and sex matched controls was studied by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. The Odds ratio (OR) with 95% confidence interval and p-value were evaluated to get the level of association of polymorphisms with risk of GI cancer, where $p \leq 0.05$ was considered as statistically significant. **Results:** After the regression analysis the results of genetic polymorphisms of *CYP17* and *CYP2C19* showed significant deviation from Hardy-Weinberg equilibrium for variant genotype of *CYP2C19*2* (rs4244285) (OR=3.37 95% CI: 1.74-6.53; p=0.0003) which indicated functional association of CYP2C19*2 with GI cancer risk in the studied population. Similarly when we studied the association of *CYP2C19*3* and *CYP17* polymorphism, the variant genotypes did not show association with development of GI cancer among rural population of south-western Maharashtra. **Conclusion:** The findings obtained from this study signified evident association of rs4244285 SNP of *CYP2C19*2* with GI cancer risk in the studied rural population.

Keywords: Gastrointestinal Cancer- *CYP7- CYP2C19*- Genetic polymorphism- cancer risk

Asian Pac J Cancer Prev, **26 (2)**, 391-398

Introduction

Gastrointestinal (GI) cancer is the most common concern and fourth leading cause of cancer deaths globally where 5.1million new cases and 3.4 million cancer causing deaths occurred in 2022 and predicted to increase 60% to 75 % in next twenty year. The incidence of GI cancer has increased highest in Asian countries with 2.9 million new cases and 2.0 million mortality reported due to GI cancer [1]. In recent years burden of GI cancer is immensely increased in India with incidence and deaths due to different cancer sites of GI tract including esophagus, (70, 637 new cases and 66, 410 deaths), colorectum (70, 038 new cases and 40, 993 deaths), stomach (64, 611new cases and 57727 deaths), gallbladder (21,780 new cases and 16, 407 deaths), and pancreas (13661 new cases and 12, 759 deaths) [1]. Diet, lifestyle, tobacco and alcohol consumption are the well recognized risk factors for etiology of GI cancer along with infection of Hepatitis B virus (HBV) and Helicobacter pylori [2-4]. On the same line, along with the interactive environment genetic background of an individual is key element for carcinogenesis [5-6], however more efforts are needed to explore association of genetic factors with GI cancer development. Genetic susceptibility of an individual towards carcinogenesis is determined by DNA modifications in the form of single nucleotide polymorphisms (SNPs) of genes involved in different cellular processes. Cytochrome P450 (*CYP450*) is an important phase-I detoxification enzyme system

*[1]Department of Molecular Biology & Genetics, Krishna Institute of Allied Sciences, Krishna Vishwa Vidyapeeth "Deemed to be University", Taluka-Karad, Dist- Satara, Pin-415 539, (Maharashtra) India. [2]Department of Oncology, Krishna Vishwa Vidyapeeth "Deemed to be University", Taluka-Karad, Dist- Satara, Pin-415 539, (Maharashtra) India. *For Correspondence: hodgeneticslab@kvv.edu.in*

accountable for metabolism of extensive endogenous substances and harmful xenobiotics, conventional drugs and environmental carcinogens from human body [7-8]. *CYP450* gene superfamily is highly polymorphic where the variants of *CYP1A1, CYP1B1, CYP2C9, CYP2C19, CYP2D6, CYP2E1* and *CYP17* can alter the gene expression thereby increasing cancer susceptibility [7, 9].The polymorphic variant alleles of *CYP2C19* and *CYP17* are recognized for their susceptibility towards variety of cancer but several other studies revealed contradictory results on the topic of cancer susceptibility.

CYP2C19 is a member of *CYP450* metabolic enzyme family involved in detoxification of many carcinogens and elimination of endogenous compounds. The functional polymorphism of *CYP2C19* gene with two commonly studied SNPs; *CYP2C19*2 CYP2C19*3* with poor metabolizer (PM) phenotype evidenced their association with various cancers including digestive system cancer in different ethnic groups [10-12] however, some other existing studies deferred their results with inconsistent outcomes. Similarly, *CYP17* is another important member of CYP gene family which encodes cytochrome p450c17α enzyme involved in the steroid biosynthesis pathway and susceptible for cancer of endocrine system including gastrointestinal tract. The functional polymorphism of *CYP17* gene may elevate or decline the levels of hormone synthesis which may lead to cancer progression [13-14]. Various epidemiological studies addressed an association *CYP17* (rs743572) polymorphism with risk of multiple cancers [14-16], but other studies disagree with their contribution in carcinogenesis [17-18]. GI cancer is a major concern of cancer causing deaths in rural parts of India with low socioeconomic demography. In view of literature, when we considered the polymorphisms in xenobiotics detoxifying genes and their association with GI cancer development, we found lack of studies on the significance of the polymorphisms in metabolic *CYP* genes including *CYP2C19* and *CYP17* with GI carcinogenesis in Maharashtra. Therefore, along with the polymorphism of *CYP2C19* gene, we assumed that *CYP17* may be relevant to identify the etiology of GI cancer in a rural population, and in this way we performed a hospital based case-control study to explore the effect of polymorphisms of these genes on the risk of GI cancer in subjects residing to rural areas of south-western Maharashtra. The polymorphisms of *CYP2C19* including *CYP2C19*2* (681G>A, SNP: rs4244285) and *CYP2C19*3* (636G>A, SNP: rs4986893) and *CYP17* gene (SNP: rs743572) from 200 patients with GI cancer and equal number of controls were assessed to see their association with GI cancer risk in a population of south-western Maharashtra region of India.

Materials and Methods

Selection of study subjects

This case control study was performed with two hundred clinically confirmed GI cancer cases and equal number of healthy, disease free, age and sex matched controls. The sample size was calculated by the formula n= [(p1xq1) + (p2 x p2)] X (Z1-α/2) +Z1-β)2/ (p1-p2)2; Where p1- presence of allele1, q1- absence of allele1, p2- presence of allele 2, q2- absence of allele 2, α- probability of detecting false results, β- power. Cases ranged in age from 20-85 years (Mean ± SD) (59.0 ±13.32) enrolled immediately after diagnosis at Krishna Hospital and Medical Research Centre during the year 2018-2021 (Table 1). Written informed consent was obtained from all eligible cases and controls who agreed to participate after being given a detailed description of the study. The structured questionnaire was prepared to collect demographic and other clinical data. The study protocol (IEC-164/2017-2018) was approved by Institutional Ethics Committee of Krishna Institute of Medical Sciences 'Deemed to be University', Karad.

Blood Sample Collection and Genomic DNA Extraction and Purification

Five milliliter (mL) of whole blood from 200 patients

Table 1. Distribution of Selected Demographic Variables of GI Cancer Cases and Healthy Cancer Free Controls

Variable		Cases (n=200) (%)	Controls (n=200) (%)	Chi Square (X^2)	p-value based on X^2
Age yrs (Mean ± SD)		59 ±13.32	57.56 ±10.69		
Age	≤50 yrs	51 (25.5)	37 (18.5)	2.85	0.09
	≥50 yrs	149 (74.5)	163 (81.5)		
Gender	Male	113 (56.5)	100 (50.0)	1.69	0.19
	Female	87 (43.5)	100 (50.0)		
Education	No School	162 (81.0)	114 (57.0)	26.92	0.0001
	School	38 (19.0)	86 (43.0)		
Diet	Vegetarian	36 (18.0)	49 (24.5)	2.52	0.11
	Mixed	164 (82.0)	151 (75.5)		
Economic status	Poor	159 (79.5)	150 (75.0)	1.15	0.28
	Rich	41 (20.5)	50 (25.0)		
Tobacco Smoking	Yes	134 (67.0)	67 (33.5)	44.89	0.0001
	No	66 (33.0)	133 (66.5)		
Alcohol Drinking	Yes	38 (19.0)	10 (5.0)	18.56	0.0001
	No	162 (81)	190 (95.0)		

*, indicates significance p<0.005; p value determined based on Chi square ($\chi 2$)

was collected in sterile EDTA containing vacutainer after receiving informed consent. Genomic DNA extraction was carried out from the peripheral blood sample using HipurA®Blood genomic DNA miniprep purification kit. (Cat no. MB504-250PR) (HiMedia Laboratories) following the manufacturer's instructions. This pure genomic DNA was used for genotyping assays by polymerase chain reaction (PCR) and Restriction fragment Length Polymorphism (RFLP).

Genotyping assays of CYP2C19 and CYP17 genes

The genotyping of *CYP2C19*2, CYP2C19*3*, and *CYP17* genes was performed by PCR-RFLP. The PCR amplification were carried out separately in 20 micro liter (μL) reaction mixtures containing 1X PCR buffer 0.2 mM each dNTP, 10 picomole (pmol) of each primers (IDT technologies) , 1U Taq DNA polymerase (GeNei, Merck Bioscience) and 100 nanogram (ng) of purified genomic DNA. The primer sequence used to amplify the *CYP2C19* and *CYP17* genes and the PCR conditions are shown in Table 2. After performing PCR programme for each reaction, the PCR products were analyzed by agarose gel electrophoresis in Tris-Acetate-EDTA (TAE) buffer. After confirmation of DNA amplification, each PCR product was digested with an appropriate restriction enzyme with specific conditions for genotyping. Ten micro liters of the PCR products digested at 37°C overnight with specific restriction enzymes in 20 μL reaction mixtures containing buffer supplied with each restriction enzyme (Table 2). After the overnight incubation, digestion products were separated on a 2-3% low EEO agarose (GeNei) gel at 100 V for 30 min stained with ethidium bromide and photographed with Gel Documentation System (BioRad).

Statistical Analysis

The association between the *CYP2C19*, *CYP17* genotypes and risk of developing GI cancer was studied by Odds ratio (OR). Logistic regression model was used to calculate the OR and 95% confidence intervals (CI) with adjustment of variables to determine the GI cancer risk associated with genotypes. All p values were two-sided and differences were considered statistically significant for $p \leq 0.05$. All statistical analyses were performed with SPSS (IBM Version 11.0) software.

Results

Characteristics of selected demographic variables

Distribution of demographic variables of the study subjects including GI cancer cases and untreated healthy cancer free controls represented in Table 1. The results of demographic characteristics showed no statistically significant difference between age (p=0.09) of the cases and control group, where the Mean ± SD age in years was 59±13.33 for cases and 57.46±11.64 for controls. Similarly the data analysis of cases and control group did not show significant relationships between gender (p=0.133) diet (p=0.11), economic status (p=0.28). However, significant relationship between tobacco habit [p=0.0001, x^2=44.89] and alcohol consumption [p=0.0001, x^2=218.56] was noted with the increased risk

Table 2. The List of Candidate *CYP2C19* and *CYP17* Genes Selected in the Present Study with Details of PCR and RFLP Procedures Including Primers and Restriction Enzymes and Expected Products of Selected Genes

Gene Genotype	rs number	Amino acid/ nucleotide change	Primer Sequence Forward/Reverse	PCR product size	Enzyme / Digestion conditions	Dominant (Wild type)	Heterozygous	Recessive (Variant)
*CYP2C19*2* G681A exon-5	rs4244285	Pro227Pro (G>A)	FP 5'-CCA GAG CTT GGC ATA TTG TA-3' RP 5'-GAA GCA ATC AAT AAA GTC CCG A-3'	230 bp	SmaI 37°C for 16h	121 bp 109 bp	230 bp, 121 bp 109 bp	230 bp
CYP2C19*3 G636A exon-4	rs4986893	Trp212Ter (G>A)	5'-CTG GGC TGT GCT CCC T-3' 5'-ACT TGG CCT TAC CTG GCT-3'	147 bp	BamHI 37°C for 16h	128 bp, 19 bp	147 bp, 128 bp, 19 bp	147 bp
CYP17 T-34C codon-34	rs743572	(T>C)	FP 5'-CAT TCG CAC TCT GGA GTC-3' RP 5'-GGC TCT TGG GGT ACT TG-3	459 bp	MspA1I 37°C for 16h	335 bp, 124 bp	459 bp, 335 bp, 124 bp	459 bp

Table 3. The Distribution of Genotype and Allele Frequencies of *CYP2C19*2, CYP2C19*3* and *CYP17* Gene Polymorphisms in Untreated Gastrointestinal Cancer Cases and Healthy Controls.

Gene/SNP	Genotype/ Allele	Cases (n= 200) (%)	Control (n =200)(%)	OR (95% CI)	P value
*CYP2C19*2*	GG/GG	63 (31.50)	132 (66.00)	1 (Reference)	
G681A	GG/AA	108 (54.00)	50 (25.00)	4.52 (2.88-7.09)	<0.0001*
Pro227Pro	AA/AA	29 (14.50)	18 (9.00)	3.37 (1.74-6.53)	0.0003*
exon-5	G allele	234 (58.50)	314 (78.50)	1 (Reference)	
rs4244285	A allele	166 (41.50)	86 (21.50)	2.59 (1.89-3.53)	<0.0001*
*CYP2C19*3*	GG/GG	170 (85.00)	172 (86.00)	1 (Reference)	
G636A	GG/AA	17 (8.50)	15 (7.50)	1.14 (0.55-2.36)	0.711
Trp212Ter	AA/AA	13 (6.50)	13 (6.50)	1.01 (0.45-2.24)	0.977
exon-4	G allele	357 (89.25)	359 (89.75)	1 (Reference)	
rs4986893	A allele	43 (10.75)	41 (10.25)	1.05 (0.67-1.65)	0.817
CYP17	TT/TT	89 (44.50)	87 (43.50)	1 (Reference)	
T-34C	TT /CC	89 (44.50)	92 (46.00)	0.94 (0.62-1.43)	0.791
codon-34	CC/CC	22 (11.00)	21 (10.50)	1.02 (0.52-1.99)	0.944
rs743572	T allele	267 (66.75)	266 (66.50)	1 (Reference)	
	C allele	133 (33.25)	134 (33.50)	0.98 (0.73-1.32)	0.94

SNP, Single nucleotide polymorphism; OR, Odds ratio; CI, Confidence Interval; Significance p< 0.05; *, Indicates significant Odds Ratio (p<0.05), p value determined based on χ^2

Table 4. Association between Gastrointestinal Cancer Risk and the Single Nucleotide Polymorphism Variant of *CYP2C19*2, CYP2C19*3* and *CYP17* Genes in the Recessive Model.A

Genes (SNP)	Genotype	Cases (n= 200) (%)	Control (n =200)(%)	OR (95% CI)	P value
*CYP2C19*2* G681A (rs4244285)	AA/AA + GG/AA	137 (68.50)	68 (34.00)	1 (Reference)	<0.0001*
	GG/GG	63 (31.50)	132 (66.00)	0.23 (0.15-0.35)	
*CYP2C19*3* G636A (rs4986893)	AA/AA + GG/AA	30 (15.00)	28 (14.00)	1 (Reference)	0.776
	GG/GG	170 (85.00)	172 (86.00)	0.92 (0.52-1.61)	
CYP17 T-34C (rs743572)	CC/CC+TT/CC	111 (55.50)	113 (56.50)	1 (Reference)	0.84
	TT/TT	89 (44.50)	87 (43.50)	1.04 (0.70-1.54)	

SNP, Single nucleotide polymorphism; OR, Odds ratio; CI, Confidence Interval; Significance p< 0.05; *, Indicates significant Odds Ratio (p<0.05), p value determined based on χ^2

of GI cancer in the studied population.

*Distribution of different genotypes of CYP2C19*2 (rs4244285), CYP2C19*3 (rs4986893) and CYP17 (rs743572) genes in GI cancer cases and controls*

In CYP450 gene family, *CYP2C19* is an important enzyme for metabolism of drugs and xenobiotic substances. In this hospital based case-control study, the genotypic frequency distribution of *CYP2C19*2* and *CYP2C19*3* was determined in GI cancer cases and matched with healthy controls in order to understand their association with GI carcinogenesis in rural population.

Table 5. Association between Gastrointestinal Cancer Risk and the Single Nucleotide Polymorphism Variant of *CYP2C19*2, CYP2C19*3* and *CYP17* Genes in the Dominant Model

Genes	Genotype	Cases (n= 200) (%)	Control (n =200)(%)	OR (95% CI)	P value
*CYP2C19*2* G681A (rs4244285)	AA/AA	29 (14.50)	18 (9.00)	1 (Reference)	0.09
	GG/AA +GG/GG	171 (85.50)	182 (91.00)	0.58 (0.31-1.08)	
*CYP2C19*3* G636A rs4986893	AA/AA	13 (6.50)	13 (6.50)	1 (Reference)	1
	GG/AA +GG/GG	187 (93.50)	187 (93.50)	1.00 (0.45-2.21)	
CYP17 T-34C rs743572	CC/CC	22 (11.00)	21 (10.50)	1 (Reference)	0.871
	TT/CC + TT/TT	178 (89.00)	179 (89.50)	0.94 (0.50-1.78)	

SNP, Single nucleotide polymorphism; OR, Odds ratio; CI, Confidence Interval; Significance p< 0.05; *, Indicates significant Odds Ratio (p<0.05), p value determined based on χ^2

The univariate logistic regression analysis was used to find out an association of *CYP2C19*2, CYP2C19*3* gene polymorphisms with GI cancer risk. The results of regression analysis showed significant deviation from Hardy-Weinberg equilibrium for variant genotype of *CYP2C19*2* (rs4244285) (OR=3.37 95% CI: 1.74-6.53; p=0.0003) which indicated functional association of *CYP2C19*2* with GI cancer risk in the studied population. Similarly Variant 'A' allele also significantly deviated in GI cancer cases as compared to healthy controls (OR=2.59 95% CI: 1.89-3.53; p<0.0001). The results of regression analysis of *CYP2C19* and *CYP17* gene polymorphisms and their association with GI cancer risk are represented in Table 3. When we studied frequency distribution of *CYP2C19*3* (rs4986893), we observed that AA variant genotype was not deviated in GI cancer cases than the healthy controls with (OR 1.01; 95% CI, 0.45 – 2.24; p=0.977). The corresponding allele frequency of G636A polymorphism of *CYP2C19*3* in studied population were 89.25 % for wild type (G) allele and 10.75 % for mutated variant (A) allele which indicated no association with GI cancer risk in studied population (OR 1.05; 95%CI, 0.67-1.65; p=0.817). The frequency of T/T, T/C and C/C genotypes of *CYP17* was 44.50, 44.50 and 11.00 in GI cancer cases and 43.50, 46.00, 10.50 healthy controls which indicated no significant difference was observed between cases and controls. When we studied combined effect of T/C + C/C genotypes showed also showed no association (OR= 0.96; 95% CI=0.64-1.42, p=0.840) with development of GI cancer among rural population of south-western Maharashtra. When polymorphism of variant genotypes of *CYP2C19*2, CYP2C19*3*, *CYP17* and their association with GI cancer risk was studied in a recessive genotype model, we found negative association of *CYP2C19*2* (SNP: rs4244285) (OR=0.23; 95% CI: 0.15- 0.35; p<0.0001) with GI cancer risk whereas other two genotypic polymorphism of *CYP2C19*3* (G636A) and *CYP17* (T-34C) showed no association with GI cancer risk in recessive genotype model (Table 4). The dominant model showed lack of involvement of either of *CYP2C19*2,* (OR=0.58; 95% CI: 0.31-1.08); p=0.090), *CYP2C19*3* (OR=1.00; 95% CI: 0.45-2.21); p=1.000) or *CYP17* (OR=0.94; 95% CI: 0.50-1.78); p=0.871) with GI risk in the studied population (Table 5).

Table 6. Association of *CYP2C19*2, CYP2C19*3* and *CYP17* Gene Variants with Demographic Variables Including Age of Cancer Occurrence, Tobacco Smoking and Alcohol Habits in GI Cancer Cases and Controls from Population of Maharashtra.

Gene	Genotype	Age (yrs) (Cases/Control)		Tobacco status (Cases/Control)		Alcohol drinking (Cases/Control)	
		≤ 50 N=51/89	> 50 N=149/111	Users N=134/47	Non-Users N=66/153	Users N=38/22	Non-Users N=162/178
*CYP2C19*2*	GG/GG	28/40	35/92	49/30	14/102	12/16	51/116
rs4244285	GG/AA +AA/AA	23/49	114/19	85/17	52/51	26/6	111/62
	OR (95% CI)	0.67 (0.33-8.1.33)	15.77 (8.46-29.38)	3.06 (1.53 -6.11)	7.42 (3.76-14.65)	5.77 (1.80-18.45)	4.07 (2.58-6.40)
	p value	0.257	<0.0001*	0.001	<0.0001	0.003	<0.0001
*CYP2C19*3*	GG/GG	43/77	127/95	115/39	55/133	29/21	141/151
rs4986893	GG/AA +AA/AA	8/12	22/16	19/8	11/20	9/1	21/27
	OR (95% CI)	1.19 (0.45-3.14)	1.02 (0.51-2.06)	0.80 (0.32-1.98)	1.33 (0.59-2.96)	6.51 (0.76-55.44)	0.83 (0.45-1.54)
	p value	0.72	0.936	0.638	0.484	0.086	0.56
CYP17	TT/TT	20/44	69/43	68/17	21/70	19/12	70/75
rs743572	TT/CC + CC/CC	31/45	80/68	66/30	45/83	19/10	92/103
	OR (95% CI)	1.51 (0.75-3.04)	0.73 (0.44-1.20)	0.55 (0.27-1.09)	1.80 (0.98-3.31)	1.20 (0.41-3.43)	0.95 (0.62-1.47)
	p value	0.243	0.223	0.087	0.056	0.734	0.841

SNP, Single nucleotide polymorphism; OR, Odds ratio; CI, Confidence Interval; Significance p< 0.05; *, Indicates significant Odds Ratio (p<0.05), p value determined based on $\chi 2$

*Correlation of genetic variants of CYP2C19*2, CYP2C19*3 and CYP17 gene with demographic variables associated with GI cancer risk*

The interactions between demographic variables such as age of cancer occurrence, tobacco and alcohol consumption habits with genotype frequencies of *CYP2C19* and *CYP17* gene polymorphism was studied among the GI cancer cases and healthy controls of the rural population of south-western Maharashtra. The results of genotype distributions of the selected *CYP2C19* and *CYP17* genes among the cases and controls and their interactions with GI cancer risk are summarized in Table 6. The logistic regression analysis showed that SNP rs4244285 of *CYP2C19*2* was associated significantly with GI cancer risk in homozygous or heterozygous after being adjusted for age of cancer

occurrence. When we stratified the genotypic distribution according to age of cancer occurrence, we observed G/A + A/A genotype significantly increased with increase in age <50 (OR=15.77 95% CI= 8.46-29.38; p<0.0001). Interestingly, when we studied rs743572 SNP of *CYP17* in relation to age of cancer occurrence, tobacco smoking and alcohol drinking habit which was not significantly associated with development of GI cancer in the studied population.

Discussion

Cytochrome P450 are most important component of phase I detoxification and drug metabolizing enzymes in human body and associated with metabolism and inactivation of carcinogens. The functional polymorphism of *CYP450* gene is associated with lock of enzyme activity and risk of developing different kinds of cancers [7, 9]. *CYP2C19* is one of the most important isoforms of *CYP450* enzymes plays a crucial role in metabolism of number of therapeutic agents and detoxification of potential carcinogens. The polymorphic nature of *CYP2C19* is observed to be associated with cancer susceptibility [10-12]. However, their role in GI cancer susceptibility is inadequately studied. Therefore, in current study we evaluated the association of *CYP2C19* gene with two major polymorphism including *CYP2C19*2* and *CYP2C19*3* with GI cancer in population of South-Western Maharashtra. Based on the results obtained in current study, significant association of *CYP2C19*2* was determined with GI cancer risk which was corroborated with other studies [10, 12, 19]. Similarly other investigations also reported significant association of *CYP2C19*2* variant genotype with digestive tract cancer risk in different ethnic population [10, 20]. In contrast to the findings obtained in current study another reports depicted either negative correlation of *CYP2C19*2* with cancer risk [21] or no association with cancer susceptibility including prostate [22] and breast cancer [23]. When we analyzed correlation of *CYP2C19*3* with GI cancer risk, we observed no association of this polymorphism with cancer risk which was also noted with esophagus [24], breast cancer risk [25-26]. Similarly, when we determined an association of *CYP17* (SNP rs743572) with GI cancer risk in the studied population, the results after analysis showed no association of *CYP17* polymorphism with GI cancer risk. Several other studied conferred the significant contribution of *CYP17* gene polymorphism with increased risk breast [27-28], prostate [29], and ovarian cancer [30]. Few Indian studies revealed association of polymorphic *CYP17* (SNP: rs743572) with increased risk of breast [15], prostate [31] and neck cancer risk [32] however, some other studies supported our findings with no association of *CYP17* polymorphisms with liver [33-34], prostate [35] and breast cancer risk [36-37]. To the best of our knowledge, limited number of studies have been carried out to substantiate an association of either *CYP2C19* or *CYP17* gene polymorphisms with gastrointestinal cancer risk in any of the Indian polupation. Therefore, in the present study we for the first time determined the polymorphism in allele frequencies of metabolic *CYP2C19* and *CYP17* genes and the risk of GI cancer in the rural population of Maharashtra from the western peninsular region of India. In this study, we investigated the relationship between the development of GI cancer and genetic polymorphisms in metabolic pathway cytochrome P450 genes from a pool of unexplored Maharashtra population and showed that rs4244285SNP of *CYP2C19* gene may confer the role in GI carcinogenesis in Maharashtrian population of India.

In conclusion, we conducted a case-control study to evaluate association between *CYP2C19* AND *CYP17* polymorphisms and GI cancer risk in population of south-western Maharashtra of India. According to our results, significant association was evident between *CYP2C19*2* polymorphism and GI cancer risk in the studied population. Our findings raise the discussion about the involvement of *CYP2C19* polymorphisms in GI cancer.

Author Contribution Statement

Concept: KDD, RAG, AKG Design: KDD, AKG, RAG, Experimental Studies: MNP, ALM Clinical studies: RAG, AKG Data analysis: KDD, MNP, Statistical analysis: KDD Manuscript preparation: RAG, KDD, AKG. All authors read and approved the final manuscript.

Acknowledgements

Funding statement

Authors are thankfull to Krishna Vishwa Vidyapeeth (Deemed to be University) Karad for financial assistance.

Approval

The study protocol was approved by protocol committee of Krishna Vishwa Vidyapeeth (Deemed to be University)

Declaration of Conflict of interest

The authors declare that they have no competing financial or any other conflict of interests that could have appeared to influence the work reported in this paper.

Ethics Committee Approval

The study protocol was approved by Institutional Ethics Committee of Krishna Vishwa Vidyapeeth 'Deemed to be University', Karad.

Abbreviations

GI: Gastrointestinal Cancer
CYP450: Cytochrome P 450
DNA: Deoxyribose Nucleic acid
PCR-RFLP: Polymerase Chain Reaction-Restriction Fragment Length Polymorphism
SNP: Single Nucleotide Polymorphism
OR: Odds Ratio
CI: Confidence Interval

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