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ORIGINAL ARTICLE

Investigating the association between rs6983267 polymorphism and susceptibility to gastrointestinal cancers in Iranian population

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Abstract

Genome-wide association studies have revealed that some single nucleotide polymorphisms at 8q24, such as rs6983267, might be effective in susceptibility to various cancers in different populations. Therefore, rs6983267 might be useful as a marker for multiple cancers. In this study, we considered a population, including 478 gastrointestinal cancer cases from the Iranian population, to investigate the association between rs6983267 and susceptibility to gastrointestinal cancers. The samples were genotyped using the TaqMan real-time PCR method while 10% of them were also confirmed by sequencing. Higher frequency of G allele was associated with higher grades of tumors in esophageal cancer and the tumors located in the lower portion of the esophagus (OR 3.56; 95% CI 1.13–11.24; $P=0.03$) and cardia (OR 5.24; 95% CI 1.26–21.83; $P=0.02$), which both locations are involved in esophageal adenocarcinomas with poor prognosis. The results indicated that in the male subgroup, the rs6983267 GG genotype significantly enhanced the gastric cancer susceptibility (OR 4.76; 95% CI 1.57–14.45; P = 0.01). GG genotype also increased the risk of intestinal-type gastric cancer, located in non-cardia (OR 4.62; 95% CI 1.25–17.04; $P=0.02$). Moreover, gastric cancer cases and controls with a family history of gastrointestinal tumors were mostly genotyped with the G allele (OR 3.61; 95% CI = 1.09–12.01; $P=0.04$). There were no remarkable associations between rs6983267 and susceptibility to esophageal and colon cancers in the Iranian population. However, different genotypes of rs6983267 had significant correlations with tumor grade, cancer type, and family history of gastrointestinal cancers. Further investigations in a larger population and other ethnicities are required to confirm these results.

Keywords Gastrointestinal cancers · 8q24 · Rs6983267 · Polymorphism · *CCAT2*

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Introduction

Gastrointestinal cancers account for a significant cause of cancer-related morbidity and mortality worldwide [1]. Esophageal and gastric cancers are considered as the eighth [2] and fifth [3] most common cancers in both sexes in the world, respectively. Esophageal cancer is classified into two major types. Esophageal squamous cell carcinoma (ESCC) usually develops in the upper and middle portions of the esophagus and is more common than esophageal adenocarcinoma (EAC), which is found in the distal esophagus [2]. Considering the tumor site, gastric cancer includes two types of cardia and non-cardia [4], while the second one is the most common type in the world [5]. This cancer is also classified into intestinal, diffuse, and mixed types by histological classification [6]. Colorectal cancer is the third most deadly cancer in females and males worldwide [7]. The main problems associated with these cancers are the late diagnosis and limited effective therapeutic methods, which lead to poor prognosis and lower overall survival rates [8].

Carcinogenesis is a complicated process involving various environmental and genetic factors. Multiple risk factors have been identified through epidemiological studies for gastrointestinal cancers, including smoking, taking drugs, alcohol consumption, unhealthy diet, and *Helicobacter pylori* infection [3, 7, 9, 10].

In addition to high penetrance genetic mutations [11, 12], low penetrance genetic factors such as single nucleotide polymorphisms (SNPs) are also associated with susceptibility to different malignancies as well as gastrointestinal cancers [13, 14]. Genome-wide association studies (GWAS) in diverse populations have revealed that 8q24, a 600-kb gene-poor region, harbors susceptibility SNPs for multiple cancers such as prostate [15–17], bladder [18], breast [19], gastric [14, 20], colorectal [16, 21], thyroid [22], lung [23], ovarian [16], and liver cancers [24]. Rs6983267, located on 8q24, significantly increases the risk of various tumors such as colorectal [21, 25, 26], prostate [17, 25], thyroid [22], lung [23], ovarian, bladder, kidney, and gastric cancers [27]. Therefore, it can be a potential marker for predicting susceptibility to various malignancies. Finding promising biomarkers for gastrointestinal pathogenesis would not only improve cancer diagnosis and prognosis but also leads to new therapeutic approaches.

In this study, the correlation between a well-known GWAS-identified SNP and cancer risk, grade, tumor location, cancer type, and family history of gastrointestinal cancers was investigated in the Iranian population.

Materials and methods

Study population

The samples, including 135 esophageal, 170 gastric, and 173 colorectal cancer cases were obtained from several hospitals in Mashhad, between June 2017 to September 2018. Two hundred ethnically-matched healthy volunteers were also included as the control group at the same time. Individuals with a family history of cancer in first degree and/or second degree relatives were excluded from the controls. All the participants were heritably Persian from the same geographical region of Mashhad, the capital of Khorasan Razavi province, which is located in the north-east of Iran. The study procedure was approved by the ethics committee of Mashhad University of Medical Sciences with reference number 1397/028.

Epidemiologic data collection

A family report of cancer and the medical history of some serious illnesses like diabetes, heart, and autoimmune diseases were carefully evaluated in both case and control groups using an adequate standard questionnaire. Other influential parameters including age, gender, race, occupational history, education, smoking, taking drugs, alcohol consumption, diet, coffee and tea drinking, clinical symptoms, cancer type, grade, and location of tumors were also recorded for each subject.

DNA extraction

600 µl peripheral blood samples were collected from all cases and controls in blood collection tubes containing K3EDTA (Greiner Bio-One, Austria), and stored at − 80 °C. Genomic DNA was extracted as soon as possible following the protocol devised by Bartlett and White [28] with some modifications. The purity and concentration of DNA samples were verified using a NanoDrop (Thermo Fisher Scientific, USA).

SNP genotyping using TaqMan probe

SNP genotyping was accomplished using the TaqMan real-time PCR (polymerase chain reaction) method (Bio-Rad CFX96, USA). The region including SNP (105 bp) was amplified using the specific primers, forward: 5′ CCT ACCACTAAGAGGTGTAGC 3′ and reverse: 5′ GTCAAT AGCACATAAAAATTCTTTGTA 3′, with binding probes 5′ TTCTCAGTGTCTTTCATCTGC 3′, labeled with FAM and 5′ TTCTCAGTGCCTTTCATCTGC 3′ labeled with

CY5 fluorophores to detect the specific alleles [29]. After an initial denaturation step at 95 °C for 15 min, the thermal cycling of denaturation at 95 °C was done for 10 s followed by 45 s of annealing and extension at 63 °C for 50 cycles. Several samples with different genotypes were selected and sequenced (Macrogen, Korea) as quality controls, which were used to confirm the subsequent results of real-time PCR.

Statistical analysis

All statistical analyses were performed using SPSS software, version 25 (SPSS, USA). The frequency of age, gender, smoking status, and taking drugs were compared between cases and controls. Hardy–Weinberg equilibrium (HWE) was evaluated in the control group using Chi-square. This test was also used to determine allele and genotype distribution in cases and controls, while $P < 0.05$ was considered as statistically significant. The allele with lower frequency was coded as the minor allele. Logistic regression was employed to distinguish odds ratios (ORs) with 95% confidence intervals (CIs) for each genotype and different genetic models (recessive, dominant, and codominant).

Furthermore, the relation between genotypes and grade, tumor location, cancer type, and family history were estimated using logistic regression. Crude ORs and 95% CIs were adjusted for confounders: age, gender, smoking status, drug-taking, and family history of cancer.

Results

Demographic features of the studied population

The demographic characteristics of cases and controls participated in this study are presented in Table 1. Briefly, cases were older than controls, and there was a male predominance in both cases and controls in esophageal and gastric cancers. However, there were no significant differences in age and sex distributions between the cases and controls in colorectal cancer. Smoking and drug-taking were higher among cases compared to controls in all gastrointestinal cancers.

Hardy–Weinberg equilibrium was maintained in case and control groups. MAF (minor allele frequency) of the study was also evaluated at 0.5 (50%), as presented in Table 2.

Tumor characteristics

As indicated in Table 3 most of the tumors were in grades 1 and 2 in all cancers. Among 127 esophageal cases with available data, tumors were located in different locations including the upper (n = 11, 8.2%), middle (n = 48, 35.5%), and lower (n = 37, 27.4%) esophagus, and cardia (n = 31, 23.0%). Gastric cancer tumors in 170 cases were distributed differentially between the cardia (n = 68, 40%) and non-cardia (n = 102, 60%) types. In 59.9% of colorectal cancer cases, tumors were observed in the colon, while 26.3% were found in the rectum. In total, 34.1% of esophageal, 98.8% of gastric, and 85.5% of colorectal cancer cases were reported to be adenocarcinoma.

Table 1 Demographic features of the cases and controls used in this study for gastrointestinal cancers

Variable	Cancer type	Case	Control	*P*
Study population	Esophageal	n = 135	n = 200	
	Gastric	n = 170	n = 183	
	Colorectal	n = 173	n = 180	
Gender	Esophageal	Female: 43%	Female: 49.5%	0.24
		Male: 57%	Male: 50.5%	
	Gastric	Female: 31.2%	Female: 48.6%	0.00
		Male: 68.8%	Male: 51.4%	
	Colorectal	Female: 49%	Female: 42%	0.22
		Male: 51%	Male: 58%	
Age (year)	Esophageal	68.0 ± 12.07	49.74 ± 14.7	0.00
	Gastric	64.5 ± 12.2	52.2 ± 12.5	0.00
	Colorectal	56.4 ± 12.5	56.5 ± 15.9	0.00
Smoking	Esophageal	31.1%	15%	0.00
	Gastric	26%	15%	0.01
	Colorectal	17%	15%	0.56
Drug-taking	Esophageal	33%	5%	0.00
	Gastric	42%	7.7%	0.00
	Colorectal	12.8%	7.8%	0.11

Table 2 Hardy–Weinberg equilibrium and MAF of study for rs6983267 gene polymorphism

Polymorphism	Cancer type	Group	Hardy–Weinberg (*P*)	MAF of study
Rs6983267	Esophageal	Case	0.38	0.5 (50%)
		Control	0.83	
	Gastric	Case	0.95	
		Control	0.76	
	Colorectal	Case	0.99	
		Control	1	

Investigating the association between rs6983267 and gastrointestinal cancers

Logistic regression analyses of the rs6983267 alleles and genotypes distribution for their association with gastrointestinal cancers are shown in Table 4. Allele and genotype frequencies were not remarkably different between cases and controls. Therefore, no significant associations were detected

Table 3 Tumor characteristics in gastrointestinal cancer cases

Variable	Cancer type		%
Grade	Esophageal	Grade 1	30.4
		Grade 2	29.6
		Grade 3	13.3
		Grade 4	7.4
		Unidentified	19.3
	Gastric	Grade 1	21.8
		Grade 2	28.8
		Grade 3	14.1
		Grade 4	2.9
		Unidentified	32.4
	Colorectal	Grade 1	29.5
		Grade 2	40.5
		Grade 3	5.2
		Grade 4	1.1
		Unidentified	23.7
Tumor location	Esophageal	Upper	8.2
		Middle	35.5
		Lower	27.4
		Cardia	23
		Unidentified	5.9
	Gastric	Cardia	40
		Non-cardia	60
	Colorectal	Colon	59.9
		Rectum	26.3
		Unidentified	13.8
Cancer type	Esophageal	Adenocarcinoma	34.1
		Squamous cell carcinoma	59.2
		Unidentified	6.7
	Gastric	Adenocarcinoma	98.8
		Lymphoma	1.2
	Colorectal	Adenocarcinoma	85.5
		Squamous cell carcinoma	0.5
		Unidentified	14

between this SNP and gastrointestinal cancer susceptibility in the Iranian population. Furthermore, as presented in Table 5, genetic models were also tested for all types of cancers, but none of them were appropriate for gastrointestinal cancers.

Stratification analysis

Genotype–phenotype analyses were performed for gender, smoking, drug-taking, grade, tumor location, cancer type, and family history; and the results are presented in Table 6.

Stratification analysis by gender indicated that in the male subgroup, rs6983267 GG as a risk genotype compared to TT (OR 4.76; 95% CI 1.57–14.45; $P=0.01$) significantly increased gastric cancer susceptibility, however, this SNP was not associated with esophageal and colorectal cancers in both males and females.

Chi-square analysis indicated that esophageal cancer patients with lower and higher grades of tumors, mostly genotyped with T and G alleles, respectively. Moreover, significant associations between grade and genotype were observed in esophageal tumor grades G1 (OR 0.18; 95% CI 0.06–0.58; $P=0.00$ and OR 0.21; 95% CI 0.07–0.63; $P=0.00$) and G2 (OR 3.59; 95% CI 1.11–11.58; $P=0.03$) using regression test, however, no associations were detected in stratified analyses in different grades of gastric and colorectal cancers.

A higher contribution of GG genotype was observed in the intestinal subgroup of gastric cancer in comparison with TT (OR 4.62; 95% CI 1.25–17.04; $P=0.02$). Furthermore, the effects of rs6983267 genotypes on tumor location were also investigated. Dividing patients based on clinical features demonstrated an association between rs6983267 GG genotype and tumors located in the lower portion of the esophagus (OR 3.56; 95% CI 1.13–11.24; $P=0.03$). Rs6983267 GG genotype also increased the susceptibility to non-cardia intestinal-type gastric cancer (OR 5.62; 95% CI 1.16–27.32; $P=0.03$), whereas no contributions were found for colorectal cancer. Furthermore, assessing these data indicated that in cases and controls with a positive family history of cancer, the GT genotype increased the susceptibility to gastric cancer in our studied population (OR 3.61; 95% CI 1.09–12.01; $P=0.04$).

In general, analyzing grade, tumor location, and family history represented novel findings on the probability of the G allele as a risk allele in esophageal and gastric malignancies in the Iranian population.

The relationship between environmental factors and gastrointestinal cancers

As shown in Table 7, there were significant relationships between drug-taking and the susceptibility to esophageal (OR 7.67; 95% CI 3.38–17.40; $P=0.00$) and gastric cancers (OR 7.49; 95% CI 3.76–14.91; $P=0.00$). Smoking could also increase esophageal cancer risk (OR 1.82; 95% CI 0.99–3.33; $P=0.04$). Moreover, the family history of any cancers and gastrointestinal cancers in first degree relatives, significantly increased the risk of esophageal cancer (OR 2.31; 95% CI 1.24–4.28; $P=0.01$ and OR 2.88; 95% CI 1.33–6.23; $P=0.01$). A remarkable correlation was found between the family history of gastrointestinal cancers and family history of gastric cancer in second degree relatives (OR 4.92, 95% CI 1.52–15.91, $P=0.01$). However, no clear association was observed for these variations in colorectal cancer patients. The covariates in this table were chosen according to the backward LR method.

Table 4 Logistic regression results of the rs6983267 allele and genotype distribution in gastrointestinal cancers

Cancer type	Genotype and allele	Case	Control	Crude OR (95% CI)	*P*	OR_{adj}[‡] (95% CI)	*P*
Esophageal	TT[†]	32 (23.7%)	53 (26.5%)	Reference		Reference	
	GG	41 (30.4%)	53 (26.5%)	0.78 (0.43–1.42)	0.42	0.64 (0.31–1.34)	0.24
	GT	62 (45.9%)	94 (47.0%)	0.92 (0.53–1.58)	0.75	1.03 (0.52–2.05)	0.92
	T[†]	126 (46.7%)	200 (50.0%)	Reference		Reference	
	G	144 (53.3%)	200 (50.0%)	1.14 (0.84–1.56)	0.40	1.28 (0.87- 1.88)	0.20
Gastric	TT	43 (25.3%)	37 (20.2%)	Reference		Reference	
	GG	39 (23.0%)	56 (30.6%)	1.67 (0.97–3.04)	0.09	1.57 (0.75–3.30)	0.23
	GT	88 (51.7%)	90 (49.2%)	1.19 (0.70–2.02)	0.52	1.37 (0.70–2.65)	0.36
	T	174 (51.2%)	164 (44.8%)	Reference		Reference	
	G	166 (48.8%)	202 (55.2%)	1.29 (0.96–1.74)	0.09	1.26 (0.86–1.83)	0.23
Colorectal	TT	37 (21.4%)	37 (20.6%)	Reference		Reference	
	GG	46 (26.6%)	54 (30.0%)	1.17 (0.64–2.14)	0.60	1.20 (0.64–2.24)	0.56
	GT	90 (52.0%)	89 (49.4%)	0.99 (0.57–1.70)	0.97	0.98 (0.56–1.72)	0.95
	T	164 (47.4%)	163 (45.3%)	Reference		Reference	
	G	182 (52.6%)	197 (54.7%)	1.07 (0.79–1.43)	0.68	1.07 (0.79–1.45)	0.64

[†]TT genotype and T allele served as the reference in all gastrointestinal cancers

[‡]Different factors adjusted for age, gender, smoking, drug-taking, and family history of cancer

OR odds ratio, *CI* confidence interval

Table 5 Genetic models of the rs6983267 in gastrointestinal cancers

Cancer type	Genotype	Genetic model	Combined genotypes	Frequency of combined genotypes in case	Frequency of combined genotypes in control	Crude OR (95% CI)	*P*	OR_{adj}[†] (95% CI)	*P*
Esophageal	GG GT + TT	Recessive	GG/GT + TT	41/94	53/147	1.21 (0.75–1.96)	Reference 0.44	0.64 (0.35–1.14)	Reference 0.13
	TT GG + GT	Dominant	GG + GT/TT	103/32	147/53	1.16 (0.70–1.92)	Reference 0.56	0.87 (0.47–1.60)	Reference 0.65
	GT TT + GG	Codominant	GT/GG + TT	62/73	94/106	0.96 (0.62–1.48)	Reference 0.85	0.76 (0.45–1.30)	Reference 0.32
Gastric	GG GT + TT	Recessive	GG/GT + TT	39/131	56/127	0.67 (0.42–1.09)	0.10 Reference	1.33 (0.73–2.40)	0.35 Reference
	TT GG + GT	Dominant	GG + GT/TT	43/127	37/146	0.75 (0.45–1.23)	0.25 Reference	0.69 (0.37–1.28)	0.24 Reference
	GT TT + GG	Codominant	GT/GG + TT	88/82	90/93	1.11 (0.73–1.68)	Reference 0.63	0.96 (0.57–1.62)	Reference 0.87
Colorectal	GG GT + TT	Recessive	GG/GT + TT	46/127	54/126	0.84 (0.53–1.34)	0.48 Reference	0.85 (0.53–1.35)	0.48 Reference
	TT GG + GT	Dominant	GG + GT/TT	37/136	37/143	0.95 (0.57–1.59)	0.85 Reference	0.99 (0.98–1.01)	0.92 Reference
	GT TT + GG	Codominant	GT/GG + TT	90/83	89/91	1.109 (0.73–1.68)	0.63 Reference	1.00 (0.98–1.02)	0.93 Reference

[†]Different factors adjusted for age and drug-taking for esophageal and gastric cancer, and adjusted for age for colorectal cancer

OR odds ratio, *CI* confidence interval

Discussion

Finding efficient biomarkers and molecular factors regulating gastrointestinal pathogenesis would not only have an impact on early diagnosis and better prognosis, but also can lead to novel therapeutic approaches. Emerging evidence has revealed that non-coding regions of the genome can also contribute to cancer development. In

Table 6 Stratified logistic regression analysis according to potential confounding factors of rs6983267 genotypes and gastrointestinal cancers

Variable	Cancer type		Genotype (GG/TG/TT)	Crude OR (95% CI)	*P*	OR_{adj} [†] (95% CI)	*P*
Gender	Esophageal	Male	GG/TT	0.95 (0.40–2.22)	0.90	0.93 (0.29–2.93)	0.90
			GT/TT	0.95 (0.46–1.98)	0.90	0.96 (0.36–2.57)	0.93
		Female	GG/TT	0.58 (0.25–1.35)	0.21	0.48 (0.18–1.30)	0.15
			GT/TT	0.93 (0.41–2.12)	0.87	1.32 (0.47–3.71)	0.59
	Gastric	Male	GG/TT	2.42 (1.06–5.50)	**0.04**	4.76 (1.57–14.45)	**0.01**
			GT/TT	1.59 (0.77–3.27)	0.21	2.37 (0.93–6.05)	0.07
		Female	GG/TT	1.06 (0.42–2.70)	0.90	0.66 (0.20–2.17)	0.50
			GT/TT	0.94 (0.40–2.21)	0.90	0.87 (0.28–2.70)	0.81
	Colorectal	Male	GG/TT	1.56 (0.66–3.69)	0.32	1.57 (0.64–3.83)	0.32
			GT/TT	1.31 (0.60–2.84)	0.50	1.35 (0.60–3.03)	0.46
		Female	GG/TT	0.83 (0.39–2.14)	0.91	0.99 (0.40–2.46)	0.99
			GT/TT	0.51 (0.36–1.67)	0.77	0.65 (0.28–1.50)	0.31
Smoking	Esophageal	Smoking	GG/TT	0.48 (0.10–2.23)	0.35	0.38 (0.05–2.68)	0.33
			GT/TT	0.37 (0.11–1.22)	0.10	0.33 (0.07–1.57)	0.16
		Non-smoking	GG/TT	0.83 (0.43–1.60)	0.59	0.68 (0.30–1.52)	0.35
			GT/TT	1.40 (0.74–2.63)	0.30	1.47 (0.66–3.29)	0.34
	Gastric	Smoking	GG/TT	0.79 (0.30–2.08)	0.63	0.88 (0.12–6.18)	0.90
			GT/TT	0.76 (0.34–1.74)	0.52	1.96 (0.36–10.73)	0.44
		Non-smoking	GG/TT	2.06 (1.06–3.99)	**0.03**	1.73 (0.76–3.97)	0.19
			GT/TT	1.42 (0.79–2.54)	0.24	1.25 (0.60–2.62)	0.55
	Colorectal	Smoking	GG/TT	1.00 (0.14–7.10)	0.99	2.55 (0.23–28.63)	0.45
			GT/TT	1.25 (0.23–6.70)	0.79	2.06 (0.20–21.22)	0.54
		Non-smoking	GG/TT	1.22 (0.65–2.32)	0.53	1.19 (0.62–2.29)	0.59
			GT/TT	0.97 (0.54–1.72)	0.91	0.91 (0.51–1.65)	0.77
Drug-taking	Esophageal	Positive	GG/TT	3.54 (0.32–39.14)	0.30	0.63 (0.03–14.30)	0.77
			GT/TT	3.71 (0.40–34.44)	0.25	0.92 (0.06–14.58)	0.95
		Negative	GG/TT	0.61 (0.30–1.22)	0.16	0.51 (0.23–1.14)	0.10
			GT/TT	0.78 (0.41–1.49)	0.46	0.85 (0.40–1.79)	0.67
	Gastric	Positive	GG/TT	7.86 (0.83–74.48)	0.07	9.08 (0.86–95.85)	0.07
			GT/TT	3.45 (0.41–29.28)	0.26	3.29 (0.36–29.75)	0.29
		Negative	GG/TT	1.27 (0.64–2.51)	0.49	1.22 (0.53–2.79)	0.64
			GT/TT	1.16 (0.63–2.14)	0.63	1.14 (0.53–2.42)	0.74
	Colorectal	Positive	GG/TT	5.00 (0.39–64.39)	0.22	2.73 (0.15–51.14)	0.50
			GT/TT	2.91 (0.27–31.21)	0.38	2.51 (0.15–41.82)	0.52
		Negative	GG/TT	1.07 (0.57–2.00)	0.83	1.13 (0.60–2.16)	0.70
			GT/TT	0.94 (0.53–1.65)	0.83	0.95 (0.53–1.71)	0.88

Table 6 (continued)

Variable	Cancer type		Genotype (GG/TG/TT)	Crude OR (95% CI)	*P*	OR_{adj} † (95% CI)	*P*
Grade	Esophageal	Grade 1	GG/TT	0.18 (0.06–0.56)	**0.00**	0.18 (0.06–0.58)	**0.00**
			GT/TT	0.24 (0.09–0.65)	**0.00**	0.21 (0.07–0.63)	**0.00**
		Grade 2	GG/TT	2.51 (0.80–7.89)	0.12	3.02 (0.91–10.07)	0.07
			GT/TT	2.75 (0.95–7.98)	0.06	3.59 (1.11–11.58)	**0.03**
		Grade 3,4	GG/TT	3.14 (0.87–11.37)	0.08	2.84 (0.76–10.55)	0.12
			GT/TT	2.17 (0.63–7.44)	0.22	2.07 (0.56–7.68)	0.27
	Gastric	Grade 1	GG/TT	0.78 (0.24–2.45)	0.67	1.31 (0.36–4.83)	0.68
			GT/TT	0.56 (0.22–1.43)	0.22	0.92 (0.32–2.68)	0.88
		Grade 2	GG/TT	0.80 (0.26–2.49)	0.70	0.52 (0.14–1.98)	0.34
			GT/TT	0.95 (0.38–2.34)	0.90	0.68 (0.24–1.88)	0.45
		Grade 3, 4	GG/TT	1.48 (0.38–5.71)	0.57	1.21 (0.27–5.38)	0.80
			GT/TT	1.73 (0.57–5.27)	0.33	1.38 (0.42–4.54)	0.59
	Colorectal	Grade 1	GG/TT	0.61 (0.18–2.04)	0.42	0.60 (0.17–2.13)	0.43
			GT/TT	0.60 (0.21–1.70)	0.34	0.59 (0.20–1.72)	0.33
		Grade 2	GG/TT	1.28 (0.50–3.23)	0.60	1.40 (0.53–3.67)	0.50
			GT/TT	0.66 (0.29–1.50)	0.32	0.69 (0.29–1.61)	0.39
		Grade 3, 4	GG/TT	1.06 (0.38–2.94)	0.91	0.97 (0.33–2.85)	0.95
			GT/TT	2.16 (0.89–5.22)	0.09	2.21 (0.87–5.58)	0.09
Tumor location	Esophageal	Upper	GG/TT	0.15 (0.02–1.34)	0.09	0.16 (0.02–1.55)	0.11
			GT/TT	0.46 (0.12–1.75)	0.25	0.40 (0.09–1.69)	0.21
		Middle	GG/TT	0.52 (0.19–1.42)	0.30	0.36 (0.11–1.18)	0.09
			GT/TT	0.51 (0.21–1.26)	0.20	0.51 (0.17–1.55)	0.24
		Lower	GG/TT	2.77 (0.94–8.12)	0.06	3.56 (1.13–11.24)	**0.03**
			GT/TT	0.93 (0.33–2.64)	0.89	0.90 (0.29–2.76)	0.85
		Cardia	GG/TT	1.86 (0.42–8.19)	0.41	2.09 (0.44–9.92)	0.35
			GT/TT	4.97 (1.35–18.37)	**0.02**	5.24 (1.26–21.83)	**0.02**
	Gastric	Cardia	GG/TT	1.41 (0.78–2.56)	0.25	1.77 (0.85–3.69)	0.12
			GT/TT	0.87 (0.52–1.45)	0.60	1.30 (0.68–2.49)	0.42
		Non-cardia	GG/TT	1.83 (1.13–2.96)	**0.01**	1.73 (0.96–3.13)	0.07
			GT/TT	1.44 (0.94–2.20)	0.09	1.54 (0.91–2.62)	0.11
	Colorectal	Colon	GG/TT	0.97 (0.48–1.97)	0.94	0.94 (0.45–1.96)	0.87
			GT/TT	0.81 (0.43–1.54)	0.53	0.79 (0.40–1.53)	0.48
		Rectum	GG/TT	1.46 (0.66–3.22)	0.35	1.60 (0.70–3.65)	0.26
			GT/TT	1.28 (0.63–2.58)	0.49	1.27 (0.61–2.64)	0.52
Cancer type	Esophageal	ESCC	GG/TT	1.04 (0.52–2.10)	0.90	0.81 (0.34–1.93)	0.64
			GT/TT	1.16 (0.62–2.18)	0.63	1.08 (0.49–2.39)	0.85
		EAC	GG/TT	0.44 (0.17–1.15)	0.09	0.48 (0.16–1.47)	0.20
			GT/TT	0.54 (0.22–1.34)	0.18	0.88 (0.30–2.55)	0.81
	Gastric	Intestinal	GG/TT	3.46 (1.30–9.22)	0.01	4.62 (1.25–17.04)	**0.02**
			GT/TT	1.39 (0.67–2.87)	0.37	1.66 (0.61–4.50)	0.32
		Diffuse	GG/TT	0.65 (0.16–2.67)	0.55	0.88 (0.19–4.00)	0.87
			GT/TT	0.56 (0.15–2.08)	0.39	0.90 (0.22–3.73)	0.89

Table 6 (continued)

Variable	Cancer type		Genotype (GG/TG/TT)	Crude OR (95% CI)	*P*	OR_{adj} [†] (95% CI)	*P*
Family history	Esophageal	Positive	GG/TT	0.96 (0.39–2.37)	0.93	0.23 (0.06–0.89)	0.33
			GT/TT	1.20 (0.53–2.74)	0.66	0.66 (0.19–2.26)	0.51
		Negative	GG/TT	0.66 (0.29–1.51)	0.33	0.83 (0.31–2.15)	0.70
			GT/TT	0.73 (0.34–1.55)	0.41	1.02 (0.42–2.44)	0.97
	Gastric	Positive	GG/TT	1.48 (0.55–3.96)	0.43	1.49 (0.41–5.43)	0.54
			GT/TT	1.90 (0.79–4.54)	0.15	3.61 (1.09–12.01)	**0.04**
		Negative	GG/TT	1.70 (0.74–3.89)	0.21	1.74 (0.66–4.57)	0.26
			GT/TT	0.97 (0.47–2.00)	0.93	0.92 (0.39–2.14)	0.84
	Colorectal	Positive	GG/TT	1.15 (0.38–3.53)	0.80	1.41 (0.42–4.82)	0.58
			GT/TT	0.97 (0.37–2.56)	0.95	1.08 (0.38–3.10)	0.89
		Negative	GG/TT	1.27 (0.61–2.63)	0.52	1.24 (0.59–2.61)	0.57
			GT/TT	1.17 (0.60–2.29)	0.64	1.19 (0.60–2.34)	0.62
Gastrointestinal family history	Esophageal	Positive	GG/TT	1.40 (0.37–5.28)	0.62	0.42 (0.02–7.59)	0.56
			GT/TT	1.60 (0.43–5.89)	0.48	0.57 (0.03–11.49)	0.71
		Negative	GG/TT	0.78 (0.39–1.57)	0.49	0.75 (0.32–1.72)	0.49
			GT/TT	0.86 (0.46–1.58)	0.62	1.15 (0.55–2.40)	0.72
	Gastric	Positive	GG/TT	0.82 (0.18–3.74)	0.80	0.85 (0.08–9.22)	0.90
			GT/TT	2.21 (0.59–8.26)	0.24	5.44 (0.52–56.83)	0.16
		Negative	GG/TT	1.67 (0.39–7.15)	0.49	2.10 (0.35–12.65)	0.42
			GT/TT	1.42 (0.39–5.11)	0.59	6.07 (0.96–38.42)	0.75
	Colorectal	Positive	GG/TT	1.11 (0.57–2.16)	0.77	1.13 (0.57–2.23)	0.73
			GT/TT	1.11 (0.60–2.03)	0.74	1.15 (0.62–2.12)	0.66
		Negative	GG/TT	1.41 (0.73–2.72)	0.31	1.36 (0.69–2.66)	0.38
			GT/TT	1.14 (0.62–2.09)	0.67	1.11 (0.60–2.05)	0.74

Significant *P* values are indicated in bold

[†]Different factors adjusted for age, gender, smoking, drug-taking, and family history of cancer

OR odds ratio, *CI* confidence interval

numerous genome-wide association and case–control studies, rs6983267 within *CCAT2* lncRNA on 8q24 has been introduced as a risk factor for several cancers in different ethnicities [30, 31]. This study was conducted to detect the association between rs6983267 and susceptibility to gastrointestinal cancers and their grade, tumor location, cancer type, and family history in the Iranian population, to introduce a predisposition biomarker for these cancers.

We did not observe any association between different genotypes of rs6983267 and esophageal cancer, which was in line with other publications. In similar studies conducted on 360 [32] and 218 [33] Chinese cancer cases, no correlations were found. Furthermore, two other reports on Caucasian [20] and American, African, Asian populations [24] had the same results.

Investigating the correlation between rs6983267 and gastric cancer has been reported in various studies [14, 20, 24, 27, 33–36]. Guo et al. indicated that in Chinese population, the GT genotype of rs6983267 increases susceptibility to gastric cancer as compared to the GG genotype. In contrast, other researches in Polish, American [20], Latin American [35], and Chinese [36] populations indicate different results: detecting no association between this SNP and gastric cancer in these studies may suggest that the observed association is dependent on ethnicity. Moreover, the selection of controls is an important factor; Labrador et al. indicated that employing controls with chronic gastritis history may lead to false results due to similar genetic background to gastric cancer cases [35].

The GG genotype of this SNP enhanced the susceptibility to colorectal cancer in studies with large numbers of participants. Still, no associations were found in smaller size populations with different ethnic groups such as African–American, Romanian, Chinese, and Iranian patients [26, 37–39].

Table 7 Logistic regression results indicating the association between environmental factors and gastrointestinal cancers

Variable		Cancer type	Crude OR (95% CI)	*P*	OR_{adj} † (95% CI)	*P*
Gender		Esophageal	1.25 (0.81–1.94)	0.32	0.84 (0.48–1.47)	0.54
		Gastric	2.09 (1.35–3.23)	**0.00**	1.60 (0.92–2.80)	0.10
		Colorectal	1.14 (0.75–1.73)	0.54	1.16 (0.75–1.81)	0.50
Smoking		Esophageal	2.56 (1.50–4.36)	**0.00**	1.82 (0.99–3.33)	**0.04**
		Gastric	2.17 (1.26–3.74)	**0.00**	0.93 (0.46–1.86)	0.83
		Colorectal	2.37 (1.16–4.84)	0.35	2.80 (1.31–5.99)	0.18
Drug-taking		Esophageal	9.50 (4.58–19.71)	**0.00**	7.67 (3.38–17.40)	**0.00**
		Gastric	9.31 (4.93–17.57)	**0.00**	7.49 (3.76–14.91)	**0.00**
		Colorectal	1.39 (0.67–2.88)	0.38	1.71 (0.77–3.78)	0.19
Family history of any cancers	First degree	Esophageal	2.89 (1.72–4.85)	**0.00**	2.31 (1.24–4.28)	**0.01**
	Second degree		1.06 (0.56–2.02)	0.86	1.71 (0.75–3.86)	0.20
	Total		1.94 (1.24–3.03)	**0.00**	1.99 (1.14–3.47)	**0.01**
	First degree	Gastric	1.93 (1.18–3.17)	**0.01**	1.29 (0.70–2.38)	0.42
	Second degree		1.17 (0.61–2.24)	0.65	2.22 (0.99–4.98)	0.05
	Total		1.51 (0.96–2.36)	0.07	1.69 (0.97–2.97)	0.07
	First degree	Colorectal	1.14 (0.69–1.90)	0.61	1.27 (0.75–2.16)	0.37
	Second degree		1.09 (0.48–2.50)	0.83	1.03 (0.44–2.43)	0.95
	Total		1.03 (0.65–1.62)	0.91	1.10 (0.69–1.75)	0.70
Family history of gastrointestinal cancers	First degree	Esophageal	2.79 (1.48–5.24)	**0.00**	2.88 (1.33–6.23)	**0.01**
	Second degree		0.84 (0.38–1.86)	0.67	1.06 (0.39–2.87)	0.91
	Total		1.99 (1.19–3.32)	**0.01**	2.57 (1.31–5.04)	**0.01**
	First degree	Gastric	2.20 (1.08–4.44)	**0.03**	1.70 (0.70–4.13)	0.24
	Second degree		1.54 (0.57–4.17)	0.39	4.92 (1.52–15.91)	**0.01**
	Total		1.74 (0.97- 3.13)	0.06	2.47 (1.16–5.24)	**0.02**
	First degree	Colorectal	1.34 (0.68–2.64)	0.40	1.42 (0.70–2.87)	0.33
	Second degree		0.90 (0.33–2.41)	0.83	0.89 (0.33–2.42)	0.83
	Total		1.19 (0.67–2.13)	0.55	1.28 (0.70–2.33)	0.42

Significant *P* values are indicated in bold

†Different factors adjusted for age, gender, smoking, drug-taking, and family history of cancer

OR odds ratio, *CI* confidence interval

This contradiction can be due to differences in population, sample size, or study design. For instance, considering the two studies in the Iranian population, Daraei et al. indicated this association, which was different from Haerian's report. In Daraei's research, the case group was selected from patients with no family history of cancer, and used a smaller sample size compared to Haerian work, which may have contributed to false-positive results. Furthermore, Haerian results were corrected by applying the Bonferroni procedure for multiple comparisons effect. Results can also be affected with heterogeneity in the case group [37] and ethnicity [26].

Furthermore, stratified analyses based on gender, revealed that the GG genotype of rs6983267 substantially correlated with gastric cancer in the male subgroup. On the other hand, a Chinese population-based study demonstrated that the rs6983267 GT genotype enhanced gastric cancer susceptibility in the female group [34]. Although the results suggested that rs6983267 genotypes may affect differentially based on gender in gastric cancer, no associations were observed in colorectal and esophageal cancers.

Some studies have shown that histological grades of tumor cells associate with the aggressiveness of gastric cancer. Hence, rs6983267 can be considered as a prognostic marker besides other epigenetic and genetic factors for managing the disease [40]. There was a clear relationship between rs6983267 and esophageal cancer grades in our study. Tumors genotyped with G allele were determined to be at higher grades.

We also investigated the association between this SNP and tumor location. A higher frequency of G allele was observed in tumors located mostly in the lower portion of the esophagus, which is involved in EAC with poor prognosis. Furthermore, we found that the GG genotype increased gastric cancer susceptibility in patients with intestinal-type and non-cardia tumors. Similarly, results from a Chinese population-based study indicated the association for GT

genotype, in intestinal and non-cardia gastric cancers [14], pointing to the importance of the G allele as a risk allele.

As several studies have indicated, tobacco smoking is responsible for lung, bladder [41], aerodigestive, cervical, liver, and stomach cancers [42, 43]. Our findings also suggest that a high proportion of esophageal cancer cases smoked and took drugs (Table 7). Statistical analyses indicated that drug-taking also significantly increased the risk of gastric cancer. Researches have shown that a family history of cancer correlates with the susceptibility to different cancers such as prostate, liver, gastric, esophageal, colorectal, and breast cancers [44]. Our results also revealed that a family history of cancer would increase the risk of esophageal and gastric cancers. Tartelon et al. indicated an association between the rs6983267 GT genotype in 8q24 and a family history of cancer [13]. Our findings demonstrated that controls and gastric cancer cases with a family history of different tumors had a higher frequency of rs6983267 G risk allele than others without a family history.

Considering tumor grade, cancer type, and family history, our findings suggest that susceptibility to gastrointestinal cancers might be associated with the G risk allele of rs6983267.

Despite the adequate statistical power of the current study, the sample size should be considered as a limitation. Thus, further investigations with an expanding sample size are needed in the genetic epidemiology of rs6983267 to confirm our findings.

Germline genetic polymorphisms could be promising biomarkers for cancer prognosis and response to personalized cancer therapy [45]. Hence, determining a panel of these SNPs would make the future of the diagnostic methods a non-invasive, reproducible, and cost-effective approach.

The mechanism of these SNPs in 8q24 is not entirely understood. There are several studies, which support 8q24 locus harbors cis-regulatory enhancers for MYC [46]. Mounting evidence has indicated that the G risk allele may increase the transcription of MYC proto-oncogene by enhancing the binding of the WNT-regulated transcription factor 4 (TCF4) [46–48]. TCF4 binds to both a transcriptional enhancer at the rs6983267 locus and the risk region interacting with MYC [49]. The formation of long-range chromatin loops with MYC has been shown to occur in colon, prostate, and breast cancers [47].

In conclusion, our results, which provide the first reported data on esophageal and gastric cancers in the Iranian population, suggest that rs6983267 has no significant association with gastrointestinal cancers with the exception of gastric cancer male subgroup. According to some findings, rs6983267 combined with other SNPs and loci in the haplotype might play a prominent role in susceptibility to these cancers. However, the epistatic effect of other SNPs and interactions between contracting SNPs can decrease the effect size of the studied SNP. Therefore, the inclusion of other SNPs or increasing the number of participants in each group can greatly improve the power of the study for further research.

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Author contributions MMM and ARB designed the experiments and proofread the manuscript. FK, SMAM, and ZB performed the experiments and analyzed the data. FK and SMAM also wrote the manuscript. MMM and LG financially supported this project. LG, AA, MM, AFP, AB, AET, MAK, and HR helped in providing blood samples.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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