

Original Article

Association of clinicopathological features with E-cadherin (CDH1) gene-160 C>A promoter polymorphism in Turkish colorectal cancer patients

ABSTRACT

Background and Aim of Study: The role of E-cadherin (CDH1) gene-160 C>A (rs16260) promoter polymorphism in colorectal cancer (CRC) still remains inconclusive. The aim of this study is to investigate the associations between the CDH1-160 C>A polymorphism with the susceptibility and clinicopathological development of CRC in the Turkish patients. To our knowledge, this is the first report examining the role of CDH1 polymorphism in Turkish CRC patients.

Materials and Methods: A total of 92 colorectal carcinoma cases (including 62 colon and 30 rectal cancer patients) and the corresponding adjacent normal tissues as controls were studied. The polymorphism was genotyped using polymerase chain reaction-restriction fragment length polymorphism analysis. Clinicopathological features including patient's age, gender, tumor stage, and tumor location (colon/rectum) were compared statistically with the polymorphism status.

Results: There was no significant difference in both genotype and allele frequencies of the CDH1 polymorphism between colorectal tumor cases and normal samples ($P = 0.472$ and 0.508 , respectively). Furthermore, no significant associations were observed between the CDH1 polymorphism status and age, gender, tumor stage, and tumor location of the colorectal tumor cases (all $P > 0.05$).

Conclusions: These results indicate that CDH1-160 C>A polymorphism does not contribute to the genetic susceptibility of CRC and the polymorphism may not be a direct effect on the progression of the disease in Turkish CRC patients.

KEY WORDS: Clinicopathological features, colorectal cancer, E-cadherin (CDH1)-160 C>A polymorphism, polymerase chain reaction-restriction fragment length polymorphism analysis, susceptibility

INTRODUCTION

Colorectal cancer (CRC) is one of the prevalent cancers and leading cancer-related deaths worldwide. Recently, its incidence is dramatically increasing in many developing countries including Turkey.^[1-3] In Turkey, CRC incidence is 20.6 and 13.1 in men and women, respectively. The mortality rate is 12.6 and 10.8, respectively.^[3] However, the exact etiology and pathogenesis of CRC remain unclear because CRC is a multifactorial heterogeneous disease resulting from complex interactions among genetic and environmental/lifestyle factors. Twin- and family-based studies have shown that estimated inherited susceptibility accounts for ~35% of total CRC risk although high-penetrance germline mutations account for only 6% of CRC cases.^[4,5] Genetic variants with common to rare frequency

and low-to-intermediate penetrance can contribute to an inherited predisposition to CRC.^[6]

E-cadherin (CDH1) is a member of a family of homophilic transmembrane glycoproteins expressed in almost all epithelial tissues and is responsible for calcium (Ca^{+2})-dependent cell-cell adhesion. It plays also fundamental roles in both establishing and maintaining cell polarity, cell signaling, cellular differentiation, and normal tissue morphology.^[7-9] Furthermore, CDH1 has been defined as an invasion tumor suppressor

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Anzel Bahadır¹,
Gokalp Eral²,
Metin Budak^{3,4},
Fumio
Shimamoto⁵,
Mehmet Ali
Korpınar³,
Sibel Erdamar⁶,
Handan Tuncel³

¹Department of Biophysics, Faculty of Medicine, Duzce University, Duzce, Departments of ²Biostatistics and ³Biophysics, Cerrahpasa Medical Faculty, Istanbul University, Istanbul, ⁴Department of Biophysics, Faculty of Medicine, Trakya University, Edirne, ⁵Department of Pathology, Cerrahpasa Medical Faculty, Istanbul University, Istanbul, Turkey, ⁶Department of Human Sciences, Hiroshima Shudo University, Hiroshima, Japan

For correspondence: Dr. Handan Tuncel, Department of Biophysics, Cerrahpasa Medical Faculty, Istanbul University, Istanbul 34303, Turkey. E-mail: hntuncel@istanbul.edu.tr

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in epithelial cells because it is frequently downregulated by the genetic or epigenetic alteration in the various types of epithelial cell tumors.^[9-12] CDH1 dysfunction because of allelic deletion and mutation has been reported in some of the colorectal carcinomas although its involvement is not frequent.^[13,14]

The human CDH1 gene is located on chromosome 16q22, contains 16 exons and 15 introns, and spans a region of approximately 100 kb of genomic DNA.^[15] A common single-nucleotide polymorphism (SNP) of CDH1 gene (CDH1-160 C>A; rs16260) has been identified at position -160 base pairs (bp) nucleotide upstream from transcription start site of the CDH1 gene promoter region. It has been reported that the variant A allele of promoter SNP (rs16260) decreased transcriptional activity which correlates with a lower transcriptional factor binding capacity by about 68% compared with wild-type C allele in the gene, suggesting that the A allele may reduce E-cadherin expression and increase susceptibility to epithelial cancers. Accordingly, this allelic variation may be a potential genetic marker that can help identify those individuals at higher risk for invasive/metastatic disease.^[16,17]

Many studies have investigated the association between the functional CDH1-160 C>A polymorphism and the risk for CRC susceptibility in different ethnic populations.^[17-29] However, the results remain conflicting and inconclusive. Most of these studies have reported that the CDH1 polymorphism showed no significant association with the CRC risk,^[18-24] whereas one study revealed an increased CRC risk for the -160 A minor allele carriers.^[17] Conversely, some meta-analysis studies indicated that -160 AA genotype and/or -160 A minor allele carriers provide a protective role against CRC risk in an ethnicity-dependent manner, which is especially evident Caucasian, European, and American populations.^[25-27] Interestingly, other studies have demonstrated an increased risk for CRC for the -160 C common allele.^[28,29] However, there are no reports in the literature investigating an association between the CDH1-160 C>A polymorphism and CRC susceptibility in the Turkish population.

The aim of the present study was to investigate the presence and association between the CDH1 polymorphism status and its clinicopathological features in Turkish CRC patients. To the best of our knowledge, this is the first molecular study on the relationship between the CDH1-160 C>A polymorphism and CRC susceptibility in Turkey.

MATERIALS AND METHODS

Study subjects

A total of 92 unrelated formalin-fixed, paraffin-embedded (FFPE) advanced colorectal tumor and the corresponding tumor-adjacent normal tissue specimens as controls were retrieved retrospectively from patients who had undergone surgical treatment in between January 2008 and 2012 at

the archive of Pathology Department in Istanbul University Cerrahpasa Medical Faculty Hospital, Istanbul, Turkey. Their diagnoses were confirmed by pathologists. Clinicopathological features including patient's age, gender, tumor stage, and tumor location (colon/rectum) were collected from all participants. The tumor stages were ranged from I to IV according to the 2002 tumor node metastasis (TNM) classification proposed by the International Union against Cancer TNM classification. Advanced CRC can be defined as either locally recurrent disease that is not amenable to definitive or salvage local therapy owing to its extent or prior therapy or metastatic disease (TNM, Stage IV disease) that is not amenable to potentially curative surgical resection.^[30]

Histological analysis

Histological evaluation was performed by routine procedures with hematoxylin and eosin (H and E) staining. Tumor tissues were fixed in buffered 10% formalin and embedded in paraffin. For histopathological diagnosis, 4 µm thick sections of FFPE tissues were prepared. The sections of each slide were examined for a grade of histological abnormality under a light microscope (Olympus, BX51, Tokyo, Japan) after H and E staining. Well and moderately differentiated tumors were pooled into the low-grade group and poor and undifferentiated tumors into the high-grade group.^[31]

DNA isolation

Genomic DNA was extracted from the cancerous and normal tissue specimens according to the method of Hiyama *et al.*^[32] Tumor or normal tissue samples of each patient were fixed in 10% buffered formalin and embedded in paraffin. The samples were cut into parallel 4–10 mm thick sections using sterile scissors, and DNA was extracted from these tissues with 25 mL extraction buffer including 100 mM Tris-HCl, 2 mM ethylenediaminetetraacetic acid, pH 8.0, and 400 mg/mL proteinase K at 55°C overnight. Afterward, the samples were boiled for 7 min to inactivate proteinase K. The concentration and quality of extracted DNA were measured by an ultraviolet spectrophotometer, and then, 2 mL of these extracts was used for each polymerase chain reaction (PCR) amplification.

Genotyping

The E-cadherin (CDH1, rs16260) gene-160 C>A promoter polymorphism genotyping was performed using PCR-restriction fragment length polymorphism analysis. DNA fragments were amplified using primers as follows: 5'-ATCAGAACCGTGCAGGTCCATAA-3' (upstream) and the 5'-GTTACCTGCCGCCACAG-3' (downstream) according to previously described by Park *et al.*^[33] PCR was conducted in a volume of 50 µL reaction mixture including 5.0 µL DreamTaq™ green buffer solution (×10), dNTP_{mix} (2 mM) each 5.0 µL, primers 0.5 µM, template DNA 1.0 µg, and 1.25 U DreamTaq™ DNA polymerase (Fermentase, Lithuania) with nuclease-free water to 50 µL. PCR conditions were as follows: an initial denaturation at 94°C for 1 min, then 30 cycles at 94°C for 40 s, 60°C for 40 s, 72°C for 40 s, and a final extension cycle at 72°C

for 40 s. Then, 151 bp PCR products were digested with 10 U/ μ L of Hinc II (Hind II) restriction endonuclease (Thermo Fisher Scientific, USA) at 37°C for 14 h. Digested products were determined by electrophoresis on 2.0% agarose gel stained with ethidium bromide under ultraviolet light. The wild-type C allele produced a single 151 bp fragment and the polymorphic A allele yielded two fragments of 91 bp and 60 bp.

Statistical analysis

Statistical analysis was performed using IBM SPSS statistical software version 21.00 (IBM Corp., Armonk, NY). Data were statistically described in terms of mean $\pm$ standard deviation, number of cases, and percentages. The McNemar-Bowker test was applied to assess differences in the distribution of CDH1 genotype and allele frequencies in between the colorectal tumor cases and normal tissue samples. A likelihood ratio, Yates correction for continuity, and Pearson's Chi-squared tests were used to assess the correlations of CDH1 polymorphism status with clinicopathological features of colorectal tumor tissue specimens. Besides, relationships between clinicopathological characteristics of colorectal tumor cases according to gender were evaluated by the likelihood ratio, Yates correction for continuity, and Fisher's exact tests. Statistical significance difference for all tests was accepted at $P < 0.05$.

RESULTS

Characteristics of the study subjects

The present study was performed using 92 cases of colorectal carcinoma and corresponding adjacent normal tissue samples consisting of 36 females (39.1%) and 56 males (60.9%) with a mean age of 61.12 ± 12.62 years. Type of tumors in 91 patients (98.9%) was adenocarcinoma, and the type of tumor in one patient (1.1%) is not known. The tumor was located in the colon (62 cases [67.4%]) and in the rectum (30 cases [32.6%]). Based on tumor staging criteria, 4 (4.3%) tumors were Stage II, 36 (39.1%) cases were Stage III, and 52 (56.5%) cases were Stage IV [Table 1].

When the associations of the clinicopathological characteristics in colorectal tumor cases were taken into account by gender, there was no statistically significant association between the gender and the all clinicopathological characteristics of the cases (all $P > 0.05$) [Table 2].

Results of CDH1-160 C>A polymorphism analysis

The frequencies of genotypes, i.e., CC, CA, and AA were 51 (55.4%), 39 (42.4%), and 2 (2.2%) in colorectal tumor cases and 53 (57.6%), 38 (41.3%), and 1 (1.1%) in normal samples, respectively. With regard to allele frequencies, C and A alleles were 141 (76.6%) and 43 (23.4%) in colorectal tumor cases and 144 (78.3%) and 40 (21.7%) in normal samples, respectively. There was no statistically significant difference in both genotype and allele frequencies of the polymorphism between colorectal tumor cases and normal samples ($P = 0.472$ for genotype and 0.508 for allele) [Table 3].

Table 1: Clinicopathological features of colorectal tumor cases

Parameters	Colorectal tumor cases, n (%)
Age, years (mean $\pm$ SD)	61.12 $\pm$ 12.62
≤ 57	33 (35.9)
> 57	57 (62.0)
Missing data	2 (2.2)
Gender	
Male	56 (60.9)
Female	36 (39.1)
Histopathological type	
Adenocarcinoma	91 (98.9)
Unknown	1 (1.1)
Tumor stage	
I	NA
II	4 (4.3)
III	36 (39.1)
IV	52 (56.5)
Tumor location	
Colon	62 (67.4)
Rectum	30 (32.6)

n=Total, SD=Standard deviation, NA=Not available

Table 2: Correlations of gender with clinicopathological features of the colorectal tumor cases

Parameters	Gender		P	χ^2
	Female, n (%)	Male, n (%)		
Age				
≤ 57	12 (13.3)	21 (23.3)	0.755	0.098
> 57	24 (26.7)	33 (36.7)		
Tumor stage				
I	NA	NA	0.793	0.463
II	1 (1.1)	2 (2.2)		
III	15 (16.7)	21 (23.3)		
IV	19 (21.1)	32 (35.6)		
Tumor location				
Colon	22 (24.4)	39 (43.3)	0.729	0.120
Rectum	13 (14.4)	16 (17.8)		

n=Total, NA=Not available

Table 3: Distribution of genotype and allele frequencies of CDH1 gene - 160 C>A (rs16260) polymorphism between colorectal tumor cases and adjacent normal samples

Genotypes	Colorectal tumor cases, n (%)	Normal samples, n (%)	P
CC	51 (55.4)	53 (57.6)	0.472
CA	39 (42.4)	38 (41.3)	
AA	2 (2.2)	1 (1.1)	
Alleles			
C allele	141 (76.6)	144 (78.3)	0.508
A allele	43 (23.4)	40 (21.7)	

n=Total, CC=Homozygous genotype, CA=Heterozygous genotype, AA=Homozygous genotype

Results of the association between CDH1-160 C>A polymorphism status and clinicopathological features

There were no statistically significant differences in among either age or gender of patients with the CDH1 polymorphism status in colorectal tumor cases ($P = 0.665$ and 0.692 for genotypes and $P = 0.742$ and 0.438 for alleles, respectively). When the association between the polymorphism status and clinicopathological features was evaluated in our study, a significant correlations were not observed among either their tumor stage or tumor location site (colon/rectum) with CDH1

polymorphism status in the cases ($P = 0.198$ and 0.678 for genotypes and $P = 0.550$ and 0.846 for alleles, respectively) [Table 4].

DISCUSSION

There is still uncertainty regarding the significance of the CDH1 gene-160 C>A (rs16260) promoter polymorphism on CRC pathogenesis in different ethnic populations.^[26] In this study, we aimed to examine the relationship between the CDH1 polymorphism and CRC susceptibility in Turkish patients. Besides, we investigated the association between the CDH1 polymorphism status and clinicopathological parameters such as patient's age, gender, tumor stage, and location. To our knowledge, this is the first study conducted in Turkish CRC patients that investigate the associations between the CDH1-160 C>A polymorphism with the CRC susceptibility and clinicopathological development of CRC. Furthermore, we firstly used healthy nontumoral tissue of CRC patients as controls in evaluating the association between the CDH1 polymorphism and the risk of developing CRC in our study, unlike all previous studies.^[17-29] Thus, we aimed to better understand the genotype-phenotype relationship of the CDH1 polymorphism in between colorectal tumor and normal tissue specimens and to avoid introducing substantial bias of the chosen case and control samples in the design of case-control association studies.

A number of studies have reported that the association between the CDH1-160 C>A polymorphism and CRC risk with an overall controversial outcome.^[17-29] Cattaneo *et al.* indicated an association between the -160 A allele and an increased risk of CRC with 1.66-fold in an Italy.^[17] However, Pittman *et al.* revealed that in British Caucasians, the -160 C allele was associated with an increased risk of CRC dose-dependent manner.^[29] On the other hand, some meta-analysis studies suggested that the -160 AA homozygote and/or -160 A allele play a protective role for European, American, and Caucasian

populations who develop CRC as an ethnicity-dependent manner.^[25-27] Other all studies did not find an association between CDH1 gene promoter -160 C>A polymorphism and CRC susceptibility in Brazil, England, South Korea, Germany, and China.^[18-24] We also found no significant differences in between colorectal tumor and normal tissue participants for the distributions of CDH1-160 genotype and allele frequencies in the present study ($P = 0.472$ and 0.508 , respectively), as an appropriate to the results of previous reports in the literature.^[18-24] In addition, our results did not show a significant association between gender, age, and the CDH1 polymorphism. This result may be considered that the physiological differences (gender, age, etc.) may not play a role in CRC occurrence or progression depending on the CDH1 polymorphism.

In addition, some studies have been investigated the relationship among CDH1-160 C>A genotype and clinicopathological features in different ethnic groups.^[18,20,21,23,29] Zhu *et al.* reported that the A genotype (AA homozygous and CA heterozygous) was significantly less frequent in CRC cases with high TNM Stage (III + IV) than those with low Stage (I + II) ($P = 0.008$). Furthermore, they found significantly decreased representation of A genotype in cases with lymph node metastasis ($P = 0.016$). They stated that the CDH1-160 C>A polymorphism is not associated with risk of CRC, but the -160 A genotype may exert a protective effect for tumor progression of CRC in the Chinese population.^[23] However, de Lima *et al.* stated that CDH1 AA genotype was associated with advanced metastatic disease but are not markers of lymphatic metastasis in the Brazil population.^[18] On the contrary, Tan *et al.* observed that neither their tumor stage nor location showed an association with the genetic susceptibility of the CDH1 polymorphism in the German population.^[21] Besides, other studies found also no significant correlation among CDH1-160 C>A SNP genotype and clinicopathological data such as tumor location (colon/rectum or proximal/distal), family story of CRC, age at diagnosis, or microsatellite

Table 4: Correlation between CDH1-160 C>A (rs16260) polymorphism status with clinicopathological features of the colorectal tumor cases

Parameters	Genotypes			P	χ^2	Alleles		P	χ^2
	CC, n (%)	CA, n (%)	AA, n (%)			C, n (%)	A, n (%)		
Age									
≤57	20 (22.2)	12 (13.3)	1 (1.1)	0.665	0.817	52 (28.9)	14 (7.8)	0.742	0.108
>57	30 (33.3)	26 (28.9)	1 (1.1)			86 (47.8)	28 (15.6)		
Gender									
Male	33 (35.9)	22 (23.9)	1 (1.1)	0.692	0.738	88 (47.8)	24 (13.0)	0.438	0.602
Female	18 (19.6)	17 (18.5)	1 (1.1)			53 (28.8)	19 (10.3)		
Tumor stage									
I	NA	NA	NA	0.198	6.015	NA	NA	0.550	1.196
II	2 (2.2)	1 (1.1)	1 (1.1)			5 (2.7)	3 (1.6)		
III	18 (19.6)	18 (19.6)	NA			54 (29.3)	18 (9.8)		
IV	31 (33.7)	20 (21.7)	1 (1.1)			82 (44.6)	22 (12.0)		
Tumor location									
Colon	33 (35.9)	28 (30.4)	1 (1.1)	0.678	0.776	94 (51.1)	30 (16.3)	0.846	0.038
Rectum	18 (19.6)	11 (12.0)	1 (1.1)			47 (25.5)	13 (7.1)		

n=Total, CC=Homozygous genotype, CA=Heterozygous genotype, AA=Homozygous genotype, NA=Not available

instability (MSI) status (high-frequency MSI [MSI-H] and microsatellite stable [MSS]) in British Caucasians and South Korea population.^[20,29] In our study, significant correlations were not observed among either their tumor stage or tumor location site (colon/rectum) with the CDH1 polymorphism genotypes ($P = 0.198$ and 0.678 , respectively) in Turkish colorectal tumor cases, which was consistent with results of previous studies in various populations.^[20,21,29] This shows that the clinicopathological properties regarding with the development and progression of CRC are the independent from the polymorphism according to our results. Unfortunately, we could not examine other histopathological features such as MSI status (MSS/MSI-H), tumor location (proximal/distal), and lymph node metastasis (present/absent) for CRC cases due to lacking these parameters in our study.

CONCLUSIONS

Our results provided an evidence that the CDH1 -160 C>A SNP polymorphism did not represent a risk of developing CRC in Turkish patients. Furthermore, this study demonstrated that CDH1 polymorphism was not significantly associated with clinicopathological parameters including tumor location and tumor stage in Turkish CRC patients. We suggest that the clinicopathological progression of CRC disease might not be regulated by CDH1 polymorphism. Hence, we can propose that the CDH1 polymorphism may not be used as a prognostic factor or biomarker or for genetic susceptibility to CRC in Turkey, but this suggestion needs further studies.

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Conflicts of interest

There are no conflicts of interest.

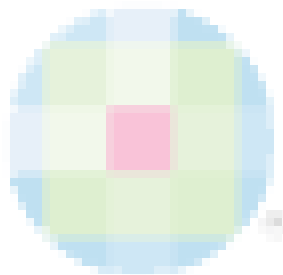
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Bahadir, *et al.*: CDH1 polymorphism in Turkish colorectal cancer patients

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