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Association of COX-2 Promoter Polymorphism with Gastroesophageal Reflux Disease (GERD) and Gastrointestinal Cancers from Iran: An Application for the Design of Early Detection of Cancer and Providing Prognostic Information to Patients in a Clinical Setting

Firouzeh Biramijamal

National Institute of Genetic Engineering and Biotechnology (NIGEB), Tehran, Iran

1. Introduction

Cyclooxygenase (COX) is a key enzyme responsible for developing several inflammatory diseases that may lead to cancer. The COX is an enzyme (EC 1.14.99.1) that it alters formation of prostanoids, including prostaglandins, prostacyclin and thromboxane. This enzyme converts arachidonic acid to prostaglandin H_2 (PGH_2) which it precursor of the prostanoids. The COX enzyme has two active sites, including heme site and cyclooxygenase site. The heme site has peroxidase activity that alters the reduction of PGG_2 (hydroperoxy endoperoxide prostaglandin G_2) to PGH_2 , and, cyclooxygenase site converts arachidonic acid into PGG_2 . It is described three COX isoenzymes, including COX-1, COX-2 and COX-3 (splice variant of COX-1). COX-1 is a constitutive enzyme and, it is expressed in most mammalian cells. Conversely, COX-2 is not expressed in most normal mammalian tissues, so, it is an inducible enzyme and it is increased in activated macrophages and during inflammation. Inflammation has central role for tumor progression. Presence of inflammatory cells can lead DNA-damage-promoting agents. Now, it is clear the relationship between inflammation and cancer. Macrophage can be produced Transforming growth factor ($TGF-\alpha$), consequential, permeability of the blood vessel and endothelium is increased in the presence of inflammation and in response to prostaglandins which is produced by COX-2 enzyme. Therefore, in this microenvironment with inflammatory cells, the extracellular matrix degradation can be occurred. Disruption of communication between the epithelium and stroma can promote cancer. Induction of Vascular endothelial growth factor (VEGF) and angiogenesis are observed after growing tumor cells, and presence of hypoxia. So, tumor cells can be received nutrients for more growth, figure 1.

COX-2 gene expression is enhanced in chronic inflammation. During prolonged inflammation, known as chronic inflammation, macrophages are produced $TGF-\alpha$ which it promote tumor growth, consequential, hypoxia is observed in microenvironment of tumor

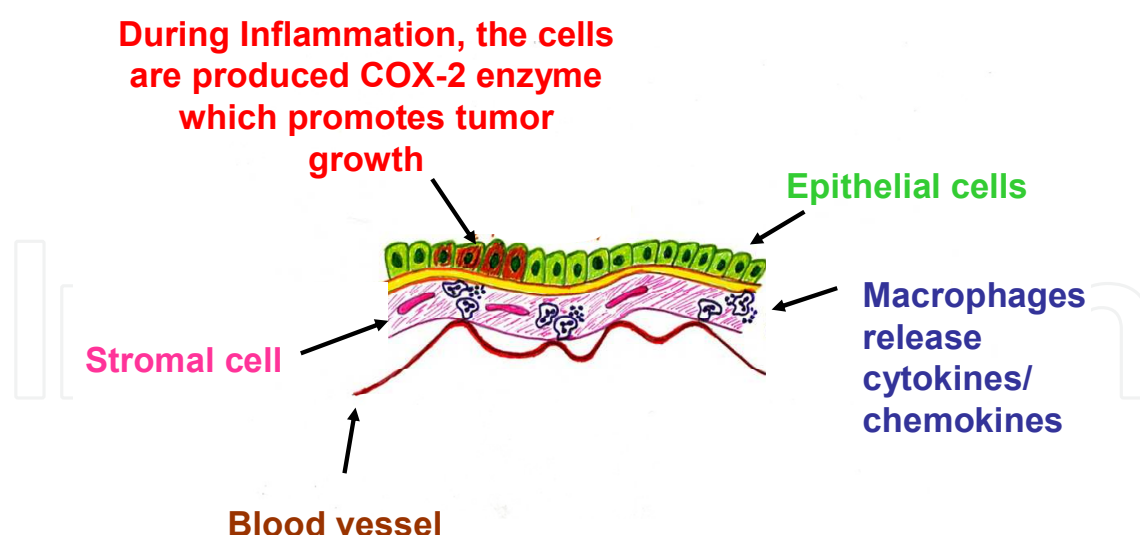


Fig. 1. Enhanced expression of COX-2 enzyme promotes tumor growth and cancer progression during prolonged (chronic) inflammation.

cells and inflammatory signals. Hypoxia is pushed the cells to produce Hypoxia-Inducible factor (HIF) which stimulates the release of VEGF. So, VEGF binds to VEGF receptors on endothelial cells, and leading angiogenesis. Also, matrix metalloproteinases (MMPs) upregulates in tumor cells microenvironment to degrade extracellular matrix proteins and tumor growth progression.

It is found that the COX-2 enzyme up-regulates in various carcinomas and it is described the role of COX-2 at an early stage in tumorigenesis. The COX-2 enzyme has been shown as an important mediator of proliferation through the increased formation of metabolites such as prostaglandin E_2 . Also, it can be increased the formation of heptanone-etheno (H ϵ)-DNA adducts which are highly mutagenic in mammalian cell lines, and accelerate the somatic mutations which are detected in tumorigenesis. It is observed that somatic mutations could be arised about 80% of various cancers.

Enhanced expression of COX-2 has been reported in many types of cancer including breast, colon, lung, pancreas, prostate, esophageal during prolonged inflammation, chronic inflammation. So, COX-2 is involved in mechanisms of carcinogenesis. COX-2 expression and activity is induced by inflammatory signals and carcinogens. COX-2 overexpression is associated with cancer development. The COX-2 gene is located at 1q25.2-q25.3.

The promoter region of the COX-2 gene consists of various transcriptional regulatory elements including stimulatory protein 1 (Sp1) binding site. The COX-2 promoter variation alters putatively functional transcription factor-binding sites. A variant at position -765 G \rightarrow C in promoter of COX-2 gene is involved in modification of COX-2 gene expression. Additionally, COX-2 -765G \rightarrow C genetic variation is linked to change the level of gene expression and serum concentrations of C-reactive protein and prostaglandin E_2 , and, inflammatory response is different among individuals with variant alleles, figure 2.

We describe in this investigation the role of COX-2 genetic variation at -765 of promoter region on the risk of gastrointestinal cancers, and also, gastroesophageal reflux (GERD) as a risk factor for developing Barrett's esophagus and then esophageal adenocarcinoma.

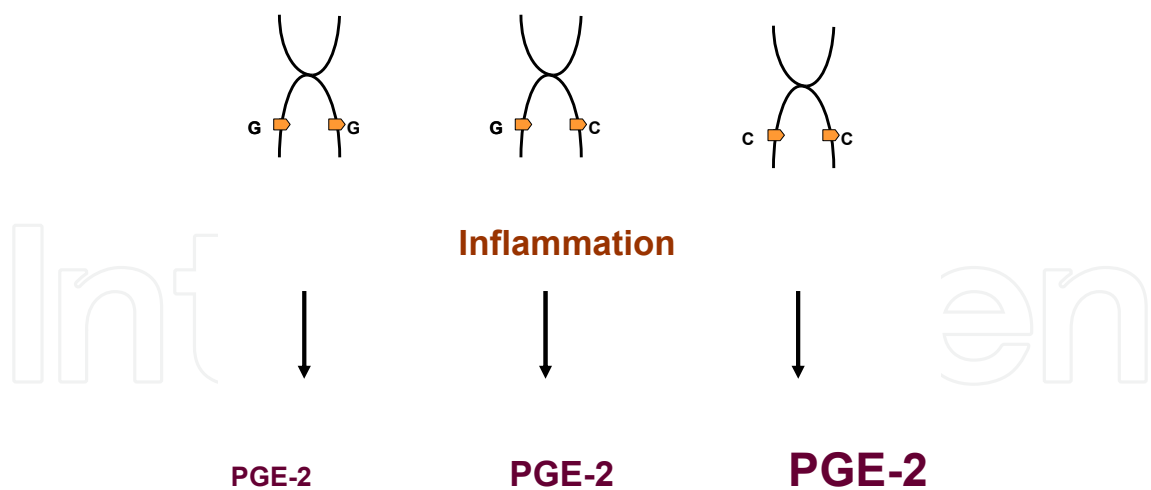


Fig. 2. Inflammatory response is different among individuals with variant alleles for COX-2 gene. The G→C substitution at -765 promoter of COX-2 gene can be changed gene expression and level of serum concentration of PGE₂.

Colorectal and esophageal cancers are frequent tumor types in gastrointestinal tract cancers. The COX-2 enzyme is known to be elevated in chronically inflamed tissues and gastrointestinal tumors. The COX-2 gene expression is dependent of interaction of nuclear proteins with the COX-2 promoter region. The promoter region of the COX-2 gene plays an important role in gene transcription. The single nucleotide polymorphisms in the COX-2 promoter can modified the binding of nuclear protein and consequentially, the level of gene expression and it can be changed susceptibility to cancer including gastrointestinal cancer.

It is described that reflux esophagitis can be changed to Barrett's esophagus (BE), and then, the risk of esophageal adenocarcinoma can be elevated 30- to 125- fold. The gastric acid reflux is the cause of esophageal damage in GERD. One of the most effective risk factors for inducing Barrett's esophagus (BE) is Gastroesophageal reflux disease. Gastroesophageal reflux disease (GERD) has been reported as a common disease worldwide. During reflux in the GERD, induction of the esophageal mucosal damage can be occurred due to inflammation. Also, chronic inflammation can be caused of progressing chronic esophagitis and premalignant Barrett's esophagus. The over expression of COX-2 gene is during chronic inflammation. It might be developed BE and adenocarcinoma (ADC) of the esophagus.

Barrett's esophagus epithelium is a premalignant condition prior to esophageal adenocarcinoma (ADC). The level of cyclooxygenase-2 enzyme is high in BE epithelium. It is shown that COX-2 gene expression is elevated 5-fold in Barrett's esophagus and 16-fold in esophageal adenocarcinoma compared to normal esophageal from healthy individuals. Additionally, it is seemed that COX-2 protein expression in the esophagus is independent of the degree of inflammation. Also, it is suggested that over expression of COX-2 can be used as a biomarker for detection of development of esophageal adenocarcinoma related to Barrett's metaplasia. The over expression of COX-2 is associated with esophageal carcinogenesis, and, the condition of tumor aggressive is dependent on the level of COX-2 protein expression.

It is reported that the individuals with -765C allele of the COX-2 gene are susceptible to esophageal cancer (both SCC and ADC lesions).

In addition, chronic inflammation can be caused of esophageal squamous cell carcinoma (ESCC) in Iran against western countries. In previous studies, it is reported that overexpression of COX-2 is approximately 70% among esophageal squamous cell carcinoma (ESCC) from Iranian patients and it is associated with p53 mutations. That investigation demonstrated the role of inflammation in carcinogenesis of ESCC in Iran as opposed to western countries. Comparing with esophageal cancer especially ESCC, the incidence of colorectal cancer (CRC) is relatively low in Iran.

In this chapter, it is described the association of COX-2 promoter polymorphism with gastroesophageal reflux disease (GERD) and gastrointestinal cancers from Iran. It might be an application for the design of early detection of cancer and providing prognostic information to patients in a clinical setting. In the next pages, it can be find some results for this aim.

2. Materials and methods

For this purpose, blood and archival cancerous human tissues from ESCC and CRC samples, also, esophageal tissue samples from GERD patients were collected. This study included 43 formalin-fixed, paraffin-embedded (FFPE) tissues from patients diagnosed with ESCC who had undergone curative surgical resection at Imam Khomeini hospital, 17 colorectal cancer tissues from patients diagnosed with adenocarcinoma who had undergone curative surgical resection at Tehran hospital. Then blood samples from eighty-two patients with at least one of three important symptoms of GERD (heart burn, acid regurgitation, or dysphagia) and erosive reflux esophagitis as diagnosed by endoscopy at the Endoscopy Ward of Fayazbakhsh Hospital (Tehran, Iran) and from 103 healthy individuals were selected.

None of the GERD patients had taken proton pump inhibitors and Nonsteroidal anti-inflammatory drugs (NSAIDs) during last 4 weeks before beginning of the study. All cases underwent treatment with omeprazole as a proton pump inhibitors (PPIs) at 20 mg twice daily for 4 weeks. At the end of treatment, second endoscopy was performed for all patients and second biopsy was obtained from the previous site.

The tissue samples from cancer patients were examined by a pathologist according to the pathological features of the tumors. Informed consent was obtained from patients and healthy individuals followed by completion of a structured questionnaire. Also, this study was approved by the National Institute for Genetic Engineering and Biotechnology. Hospital records were used to verify age, permanent residence, and ethnicity of individuals.

Genomic DNA was obtained from FFPE tissues in cases and from whole blood of patients and healthy individuals by the QIAGEN Flexigen kit or QIAamp DNA minikit (Qiagen, Valencia, CA). The extracted DNA was then kept in a -20°C freezer until further use. The COX-2 -765G → C genotyping was performed by PCR, and a fragment of 228 bp was amplified from DNA isolated from FFPE tissues and blood using

the primers COX F: 5'-CATTA ACTATT TACAGGGTAACTGCTT-3' and COX R: 5'-TGCAGCACATACATACATAGCTTTT-3'. PCR was performed in a 25- μ l volume containing 100 ng DNA template, 50 pmol each primer, 10 mM each dNTP, 2.5 μ l Q solution buffer, and 2.5 μ l coral buffer, 1 U/ μ l Taq DNA polymerase (HotStarTaq Plus PCR kit from Qiagen). Initial denaturation for 10 min at 94°C was followed by 35 three-step cycles at 94°C for 30 s, at 56°C for 30 s, and at 72°C for 30 s. The PCR products were subsequently digested with 10 U SsiI (Fermentas, Lithuania) for 3 h at 37°C and separated on a 3% agarose gel. If the CC genotype does not cut the PCR product, then there is a 228-bp fragment. If there is a GC, there is a cut site, and theoretically it should yield a 228 bp + 168 and 60 bp fragment. The GG genotype should give only a 168-bp and 60-bp fragment, figures 3 & 4. To confirm the result of PCR-RFLP, selected PCR products were subjected to DNA sequence analysis, figure 5.

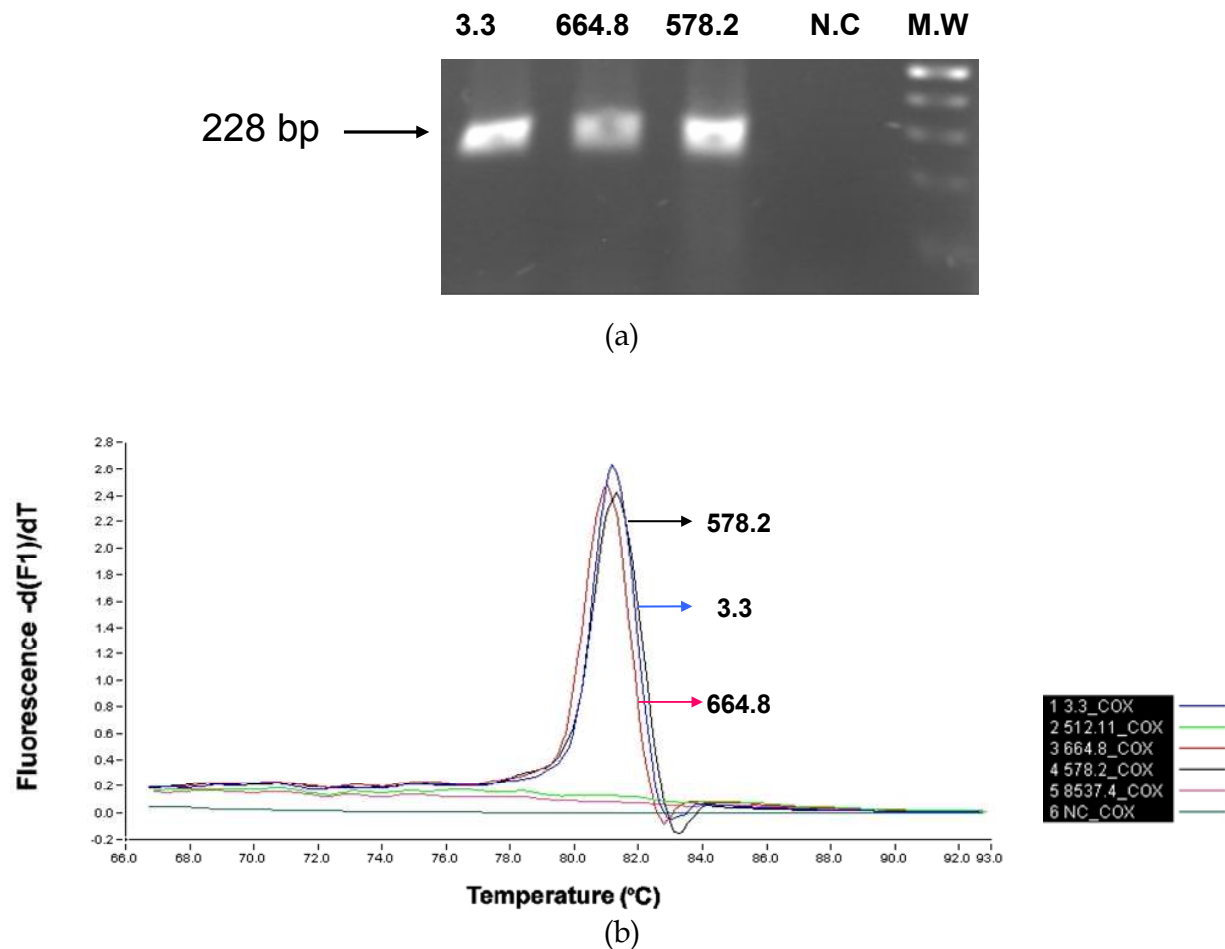


Fig. 3. A PCR assay to detect genetic polymorphism at the COX-2 promoter region. A 228 bp region of genomic DNA flanking -765 of promoter was amplified using primers which were described in the text. (A) The PCR products run on 2% agarose gel for cases numbers 3.3, 664.8, and 578.2 which were compared with negative control (NA), PCR reaction without using genomic DNA to control analysis and possibility of contamination, and a Molecular Weight marker (MW). (B) Detection of peak of PCR product with light cycler instrument to confirm exact amplification.

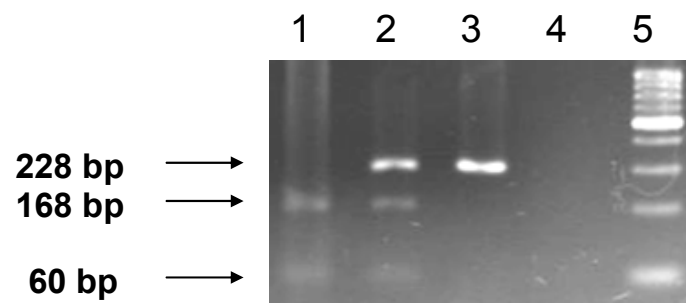


Fig. 4. Running digested PCR product with SsiI restriction enzyme on 3% agarose gel to detect of COX-2 polymorphism at -765 of the promoter region. Lane 1, sample with condition of homozygous genotype (G/G); Lane 2, sample with condition of heterozygous genotype (G/C); Lane 3, sample with condition of homozygous genotype (C/C); Lane 4, negative control (NA) to control the condition of digestion procedure using a reaction without restriction enzyme; Lane 5, Molecular Weight marker (MW).

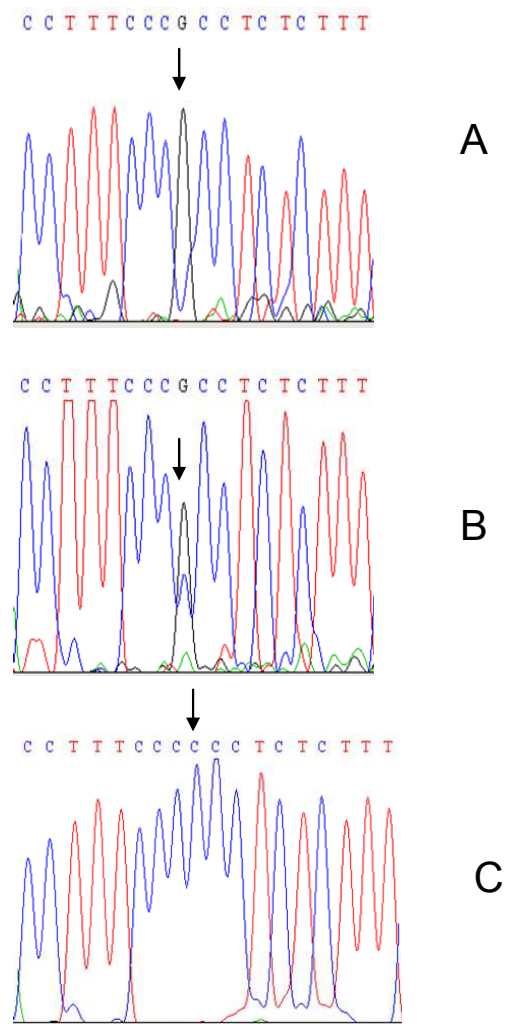


Fig. 5. Electropherogram of DNA sequencing (5'→3') showing a single base substitution (G→C) polymorphism at nucleotide -765 of promoter region. (A) homozygous wild genotype (G/G). (B) heterozygous genotype (G/C). (C) homozygous genotype (C/C).

Of the 82 esophagitis tissue samples examined in this study for the COX-2 genetic polymorphism, frozen samples of 19 patients were available for evaluation of mRNA expression for COX-2 gene. The tissues were taken from GERD patients by endoscopic biopsy, and then, the samples immersed in RNA later (QIAGEN, Valencia, CA) for RNA preservation, where the tissue-containing tubes were kept in a -70°C freezer for later use. RNA extraction was performed by the QIAGEN RNeasy Kit, and the RNA samples were kept at -70°C.

For analysis of COX-2 gene expression we used real-time PCR method by Roche Lightcycler apparatus. Real-time PCR were carried out in a 25- μ L. Reaction volume in Roche capillaries. The reaction mixture contains 0.5 μ L TaKaRa Ex.taq and 12.5 μ L TaKaRa one step Master mix, and 0.5 μ L TaKaRa RT primers and 7.5 μ L TaKaRa RNase free distilled water and forward and reverse COX-2 RT primers, each one 10 pmol/L, and 2 μ L tissue total RNA containing 250 ng total tissue mRNA. For internal control, we used β -actin for normalizing the expression values between all samples and obtaining comparative expression values relative to β -actin. Primers for the reactions were COX-2 forward: 5'-CCTTCCTCCTGTGCCTGATG -3' and reverse: 5'-ACAATCTCATTTGAATCAGGAAGCT-3', and for β actin: forward: 5'-GAGACCTTCAACACCCCAGCC-3' and reverse: 5'-AGACGCAGGATGGCATGGG-3'. For each of the real-time amplifications, we prepared a standard curve by running real-time PCR with five 10-fold diluted cDNAs as template for COX-2 and β -actin, separately. Therefore, in each run for samples we had reactions for COX-2 and β -actin for every sample and one standard sample for COX-2, one standard sample for β -actin, and also a negative control for COX-2 and a negative control for β -actin. COX-2 to β -actin comparative values were obtained as final expression values for each of the tumor tissues and the normal tissues, both for cases and healthy controls. COX-2 real-time program consisted of three phases; a reverse transcription phase for 5-10 min at 42°C, then an amplification-quantification phase of 50 cycles of one denaturation step at 95°C for 5 s and one elongation step at 60°C for 35 s, and a final phase of melting by increasing the temperature from 65°C to 100°C in 15 s.

The *P* values of COX-2 genotype comparisons between cases and control groups were considered statistically significant and were below 0.05. This measurement was made by χ^2 and Fisher's exact test. SPSS version 16 was used for all statistical analyses.

For comparison of COX-2 gene expression means, it is used the Student t-test, and ANOVA was applied for comparison of multiple groups in regard to their quantitative expression levels.

3. Results

Detection of COX-2 genotype for Cases (ESCC, CRC, and GERD/Control)

We investigated the role of COX-2 -765G→C polymorphism in a case-control study to find the distribution of allele frequencies. This polymorphism is known to modulate the transcriptional activity and expression of the gene. The study group of 142 patients included 43 ESCC, 17 colorectal cancers and 82 GERD genotyped for COX-2 polymorphism data. We assayed DNA from these samples for the frequency of allelic polymorphism at position -765G→C in the COX-2 gene. In healthy individuals, the distribution of genotypes fits the Hardy-Weinberg equilibrium. The frequency of the C allele was identical among the two

groups of cancer patients ($P=0.05$), but the distribution of the CC genotype was different in the two groups ($P = 0.001$): 23.25% (10 of 43 patients) for ESCC and 5.8% (1 of 17 patients) for colorectal cancers. Our results showed that the frequency of the C allele (GC + CC genotypes of the COX-2 gene at position -765G→C among the cancer patients and GERD patients are high compared with controls. The variation of the allele frequency among cancer and GERD groups was significantly different from controls, $P = 0.000$, and $P = 0.001$, respectively.

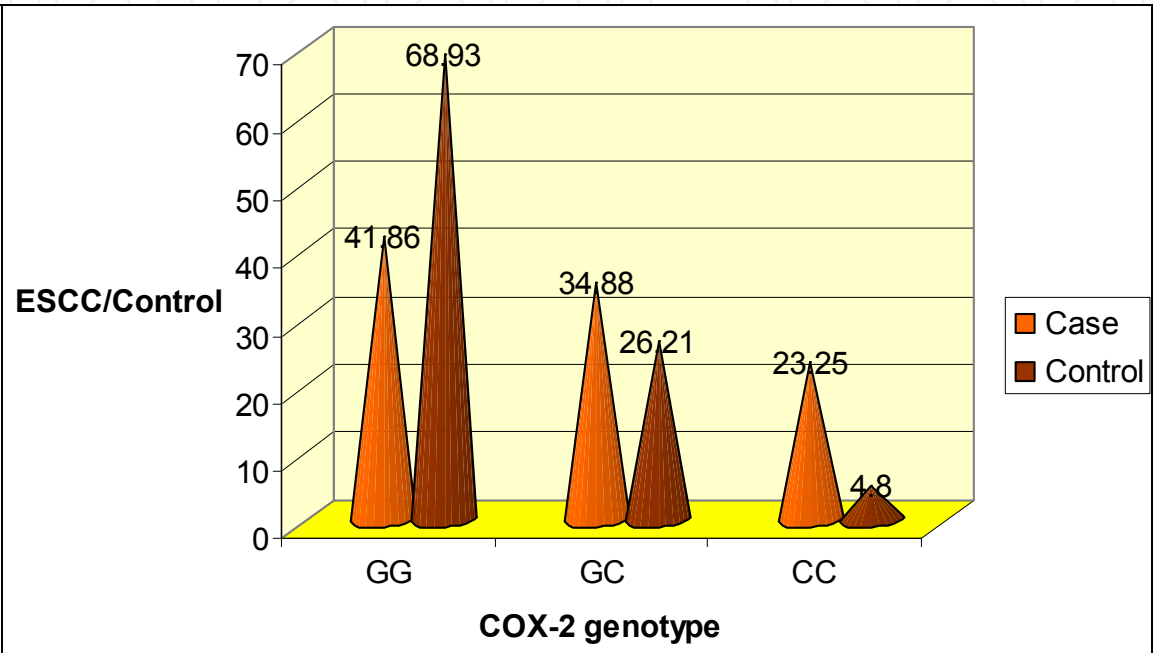


Fig. 6. Frequency of various genotypes of COX-2 gene among ESCC patients versus healthy individuals.

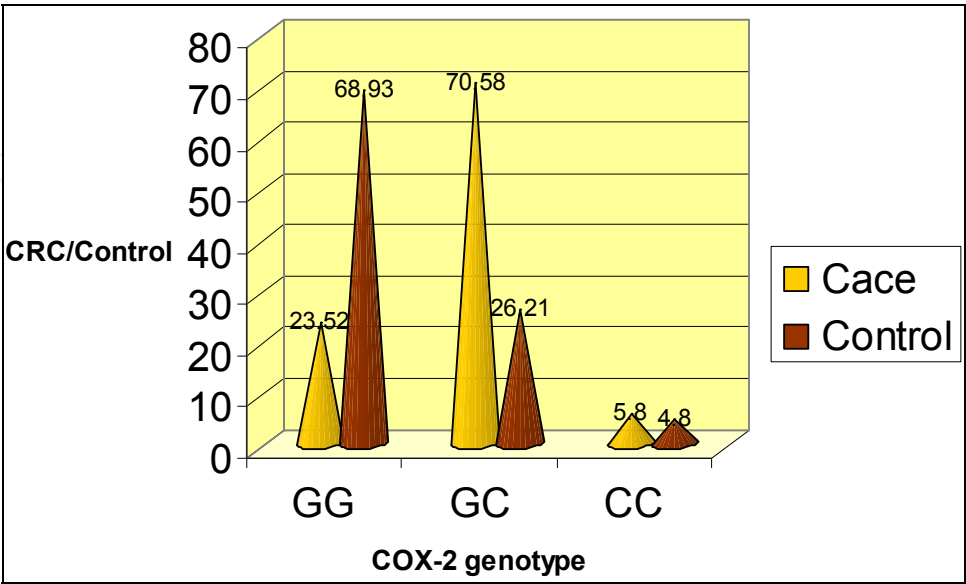


Fig. 7. Frequency of various genotypes of COX-2 gene among CRC patients versus healthy individuals.

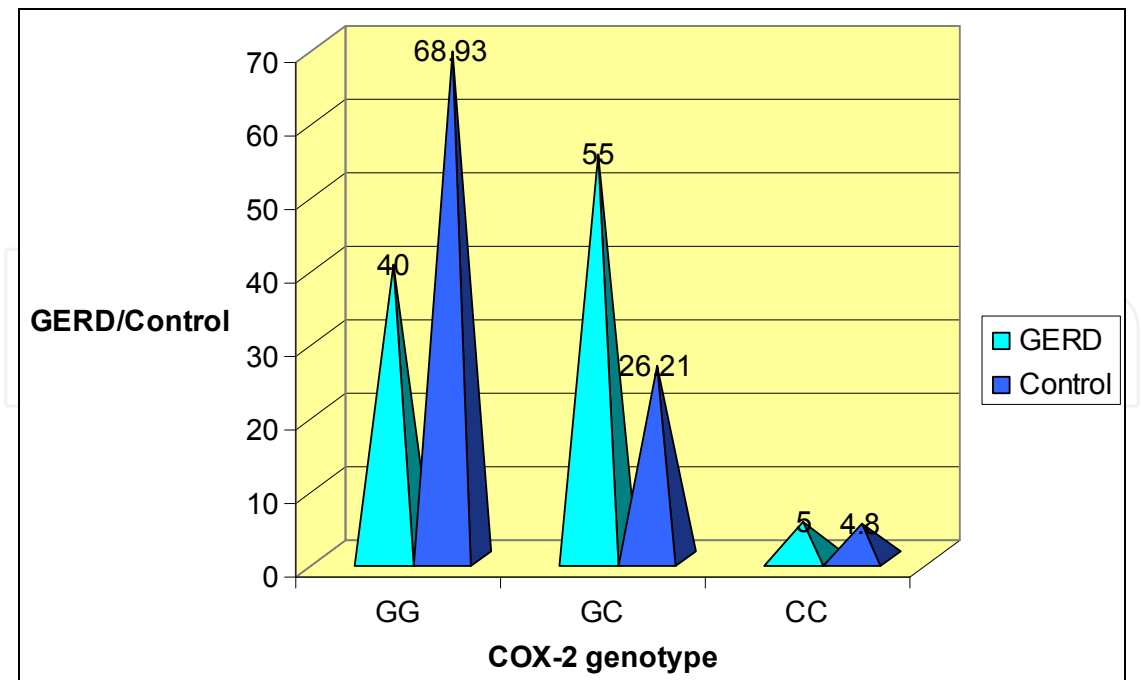


Fig. 8. Frequency of various genotypes of COX-2 gene among GERD patients versus healthy individuals.

COX-2 gene expression

Nineteen patients were enrolled in this study. We found that eight cases (42.1%) were -765GG (wild type), 10 (52.6%) were -765GC (heterozygous) and 1 (5.2%) was -765CC.

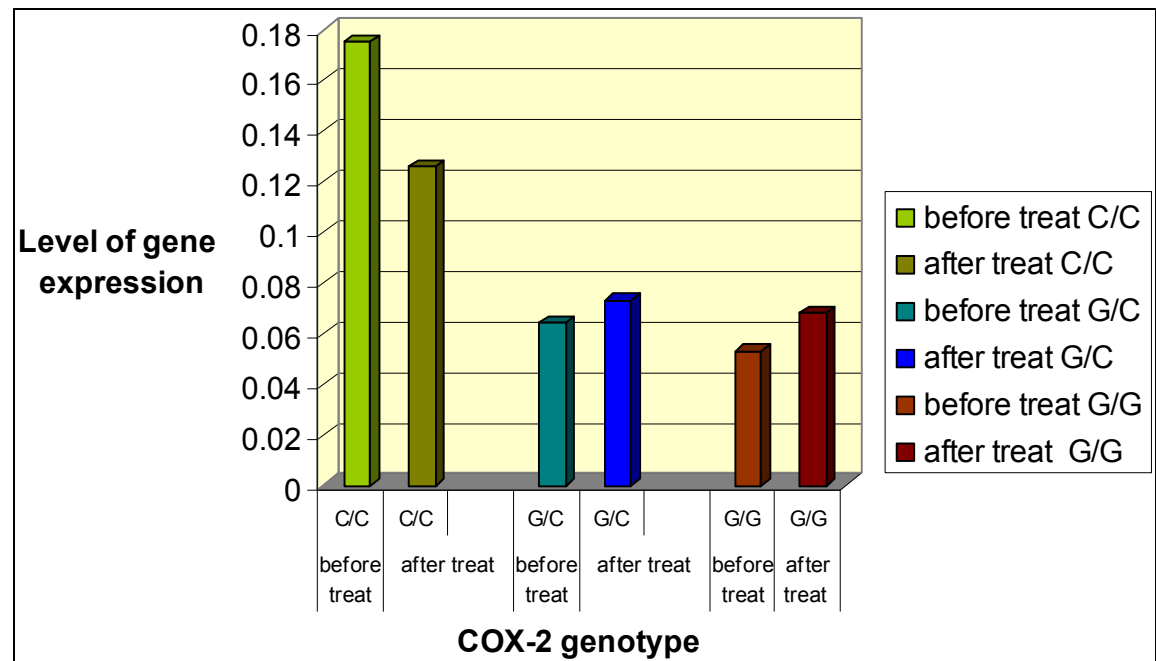


Fig. 9. Distribution of nucleotide variation at -765 promoter of COX-2 gene and its effect on level of COX-2 over expression. It is showed in this study that COX-2 overexpression is remained high among GERD patients after treatment with Omeprazole. It is assumed that C allele can be changed the activity of COX-2 enzyme against wild allele.

COX-2 mRNA expression was detectable by quantitative real-time RT-PCR in all of 38 tissue samples (were obtained from 19 patients in pre and post- treatment statuses). The over expression of COX-2 gene remained high after treatment with Omeprazole in the most of patients with GERD. The differences was identical among the two groups of investigated samples ($P=0.07$).

4. Discussion

The level of the COX-2 enzyme is elevated during inflammation, reflux esophagitis and in many types of cancers, including ESCC and colorectal cancer. In addition, it is reported that COX-2 promoter polymorphisms can modulate the expression of the COX-2 gene.

Our results in the present study showed that the frequency of the C allele (GC + CC genotypes of the COX-2 gene at position -765G→C) among the patients is high compared with controls. This investigation could clarify the importance of the COX-2 variants in reflux esophagitis and gastrointestinal carcinogenesis in Iran. Our results show that C carriers are at higher risk for GERD, ESCC and colorectal cancers. In this study, it is found that the COX-2 over expression was remained after treatment period with Omeperazole in GERD patients with C allele at site of -765 promoter for COX-2 gene. Because, it is described that the level of cyclooxygenase-2 enzyme is high in Barrett's esophagus (BE) epithelium, and also, it is shown that COX-2 gene expression is elevated 5-fold in Barrett's esophagus, so, with regard of our results, it can be assumed that the risk of BE developing in the GERD patients with COX-2 over expression, after treatment with Omeperazole, might be occurred. This hypothesis must be investigated in further study according following up the patients.

It is shown that G allele at site of -765 promoter for COX-2 gene can reduced COX-2 gene expression. Additionally, it is observed that G allele can be changed serum prostaglandin E_2 (PGE_2) concentrations. Also, the COX-2 -765G→C polymorphism was demonstrated to influence the expression of COX-2 and change the risk of developing adenocarcinoma. Chronic inflammation can be developed epithelial hyperplasia, dyslasia, adenoma and adenocarcinoma in epithelium of colorectal.

It is described that COX-2 -765C allele is a protective factor against oral squamous cell carcinoma among Taiwan population. However, the COX-2 -765 variants has not effect on the risk of head and neck carcinogenesis among Netherland population. Our results showed that carriers with C alleles are at higher risk for Gastroesophageal reflux disease (GERD), Esophageal squamous cell carcinoma (ESCC) and colorectal cancers.

It is suggested that genetic variation at -765 of the COX-2 gene may change the over expression of COX-2 and therefore result in a higher synthesis of prostaglandins affecting the Barrett's esophagus and carcinogenesis process. In addition, it is described that -765C allele of the COX-2 gene affects carcinogenesis of ESCC in Iran.

Therefore, our findings can change the direction of future study, focusing on the use of therapeutic drugs to control and decrease the risk of gastrointestinal cancers among Iranian populations. Degree of COX-2 overexpression may be used as an inducible biomarker for detection of risk of malignant transformation in GERD patients.

5. Conclusion

It is suggested that identification of COX-2 gene expression and polymorphism at -765 of promoter can be used for design of early detection of esophageal cancer and providing

prognostic information to GERD patients. Measurement of the degree of COX-2 over expression can be used as a biomarker for detection of susceptibility of malignant transformation among GERD patients.

Our study observed the association of the -765C allele carrier genotype with risk for ESCC, colorectal cancer and GERD in an Iranian population. Iran has a high incidence of ESCC in some parts (Golestan Province) and a young age distribution for colorectal cancer, and developing GERD symptoms. The results obtained from such studies can be of great importance from a therapeutic point of view, as both groups of cancer cells overexpress COX-2 and are more sensitive to COX-2 inhibitors. Further investigation of other cancer groups including ADC of the esophagus is required to compare with our results.

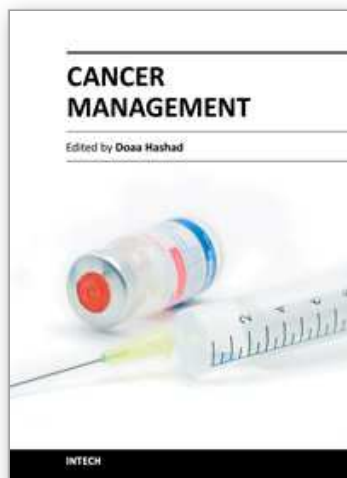
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中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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