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doi:10.3748/wjg.15.4561

World J Gastroenterol 2009 September 28; 15(36): 4561-4565
World Journal of Gastroenterology ISSN 1007-9327

COX-2 polymorphisms *-765G→C* and *-1195A→G* and colorectal cancer risk

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Received: April 21, 2009 Revised: August 26, 2009
Accepted: September 2, 2009
Published online: September 28, 2009

Abstract

AIM: To determine the possible modulating effect of the *COX-2* polymorphisms, *-765G→C* and *-1195A→G*, on the risk of colorectal cancer (CRC) in a Dutch population.

METHODS: This case-control study includes 326 patients with CRC and 369 age- and gender-matched controls. Genotypes of the *COX-2* polymorphisms *-765G→C* and *-1195A→G* were determined by polymerase chain reaction-based restriction fragment length polymorphism. *COX-2* genotypes and haplotypes were analyzed and odds ratios with 95% confidence intervals were estimated by logistic regression.

RESULTS: The *-765GG* genotype was associated with an increased risk of developing CRC (OR, 1.45; 95% CI, 1.03-2.04). No significant difference was observed in the genotype distribution of the *-1195A→G* polymorphism between patients and controls. The *GG/AC* haplotype was present significantly less often in patients than in controls (OR 0.44; 95% CI, 0.22-0.85). When the *AC*, *AG* and *GG* haplotypes were investigated separately, the *AC* haplotype showed a tendency to be less frequent in patients than in controls ($OR_{(AG/AC)}$ 0.78; 95% CI, 0.57-1.06).

CONCLUSION: The *-765GG* genotype is associated with an increased risk of developing CRC and the *GG/AC* haplotype seems to protect against CRC. These findings suggest a modulating role for the *COX-2* polymorphisms *-765G→C* and *-1195A→G* in the development of CRC in a Dutch population.

Key words: Colorectal carcinoma; Cyclooxygenase-2; Genetic polymorphism

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Hoff JH, te Morsche RHM, Roelofs HMJ, van der Logt EMJ, Nagengast FM, Peters WHM. COX-2 polymorphisms *-765G→C* and *-1195A→G* and colorectal cancer risk. *World J Gastroenterol* 2009; 15(36): 4561-4565 Available from: URL: http://www.wjgnet.com/1007-9327/15/4561.asp DOI: http://dx.doi.org/10.3748/wjg.15.4561

INTRODUCTION

Colorectal cancer (CRC) is a common disease in both men and women. CRC includes cancerous growths in the cecum, colon, sigmoid and rectum. In Western countries, 5% of the population ultimately develop CRC, thus this disease is an important public health issue[1]. CRC is ranked the third most common form of cancer worldwide in terms of incidence[2]. In the Netherlands, CRC is the second most common form of cancer affecting women and the third most common form of cancer affecting men. In 2003 in the Netherlands 9898 new cases of CRC were diagnosed[3].

CRC is usually observed in one of three specific patterns: sporadic, inherited or familial. The sporadic form accounts for approximately 70% in the population and is most common in individuals older than 50 years of age, probably as a result of interactions between low penetrance genes and environmental factors. Fewer than 10% of the population has an inherited predisposition to colon cancer. Inherited colon cancer is usually the result of a single germ line mutation. The third pattern, familial colon cancer, includes those families in which CRC develops too frequently to be considered as sporadic colon

cancer and which are not in a pattern consistent with an inherited syndrome. Up to 25% of all cases of CRC are estimated to fall into this category[1].

Cyclooxygenase (COX), also known as prostaglandin endoperoxidase H synthase, is a modifier gene and key enzyme in the conversion of arachidonic acid into prostaglandins.

The COX family consists of two isozymes: COX-1 and COX-2. COX-1 is constitutively expressed in most cell types and is involved in the homeostasis of various physiological functions. *COX-1* is well known as the housekeeping gene. COX-2 is an inducible form and its expression can be induced by mitogenic and proinflammatory stimuli. Increased expression of COX-2 is observed in many types of cancers. COX-2 is also associated with many stages of cancer development, e.g. invasion, metastasis, hyperproliferation, transformation and tumor growth[4,5].

Recent studies suggest that single nucleotide polymorphisms (SNPs) in the *COX-2* promoter may alter the enzyme function of COX-2 by differential regulation of COX-2 expression. A differential COX-2 expression may influence the risk of the development of gastrointestinal adenocarcinomas, including CRC[6-9].

In a study of African-Americans, an inverse association was found between the Val511Ala polymorphism and the risk of CRC[8]. In two studies the promoter polymorphisms *-765G→C* and *-1195A→G* were associated with an increased risk of CRC[9,10], whereas Ulrich *et al*[11] reported a reduced risk of CRC associated with the *-765G→C* polymorphism. The inconsistent results may indicate that the *COX-2* polymorphisms *-765G→C* and *-1195A→G* may play a role in carcinogenic processes in combination with specific life-style conditions or dependent on the racial composition of a particular population.

The purpose of our study was to determine the possible modulating effect of the *COX-2* polymorphisms *-765G→C* and *-1195A→G* on the risk of sporadic CRC in a Dutch population. The results of this research will lead to a better understanding on the role of SNPs in the *COX-2* promoter in colon cancer carcinogenesis. Such knowledge in future may eventually lead to better preventive measures for CRC.

MATERIALS AND METHODS

Patients and controls

This case-control study included 326 patients with CRC (59.8% men, 40.2% women) and 369 cancer-free controls (59.1% men, 40.9% women). In the patient group, 31.0% had a proximal tumor and 68.1% had a distal tumor, whereas in 0.9% of cases localization of the tumor was unknown (see legend of Table 1). All subjects were of Caucasian origin with a mean age of 63.7 years and were recruited at Radboud University Nijmegen Medical Center, the Netherlands. The patient and control groups were matched for gender and age. The characteristics of patients and controls are summarized in Table 1.

Table 1 Characteristics of patients with colorectal cancer (CRC) and controls (mean ± SD)

	Patients with CRC (n = 326)	Controls (n = 369)
Age (yr)	62.7 ± 11.7	64.5 ± 10.7
Male gender	195 (59.8%)	218 (59.1%)
Female gender	131 (40.2%)	151 (40.9%)
Localization of tumor[1]		
Proximal[2]	101 (31.0%)	
Distal[3]	222 (68.1%)	

[1]Note that the localization of the tumor was unknown in 3 patients; [2]Proximal tumor: cecum, ascending and transverse colon; [3]Distal tumor: descending colon, sigmoid, rectosigmoid junction and rectum.

Genotyping

DNA from patients and controls was isolated from whole blood using the Pure Gene DNA isolation kit (Gentra Systems, Minneapolis, MN) and stored at 4℃. Genotypes of the *COX-2 -765G→C* and *-1195A→G* polymorphisms were determined by polymerase chain reaction (PCR)-based restriction fragment length polymorphism, according to the method of Zhang *et al*[5].

First, PCR was used to amplify the *COX-2* promoter region containing the polymorphism *-765G→C* and *-1195A→G*. The primers used to amplify the *COX-2* promoter region were 765F5'-TATTATGAGGAGAATTTACCTTTCGC-3'/765R5'GCTAAGTTGCTTTCAACAGAAGAAT-3', and 1195F5'CCCTGAGCACTACCCATGAT-3'/1195R5'-GCCCTTCATAGGAGATACTGG-3'. PCR was performed using a 25 μL reaction mixture containing 100 ng of DNA, 10 mmol/L of Tris/HCl (pH 9.0), 50 mmol/L of KCl, 0.1% of Triton X-100, 2 mmol/L of $MgCl_2$, 200 nmol/L of each primer, 250 μmol/L of deoxyribonucleotide triphosphates and 2.5 U Taq DNA polymerase. The PCR profile for the *-1195A→G* polymorphism consisted of an initial melting step of 3 min at 95℃, followed by 40 cycles of 30 s at 95℃, 30 s at 58℃, 30 s at 72℃ and a final elongation step of 7 min at 72℃. Cycle conditions for the *-765G→C* polymorphism were 4 min at 95℃, followed by 40 cycles of 30 s at 95℃, 30 s at 54℃, 30 s at 72℃ and finally the same elongation step as for the *-1195A→G* PCR assay. The samples were then analyzed by agarose gel electrophoresis for control of the PCR products.

The PCR products (10 μL) were incubated with 10 U of restriction enzymes *Pvu*Ⅱ and *Hha*1 at 37℃ for determination of the *-1195A→G* and *-765G→C* genotypes, respectively. Finally, the samples were analyzed by agarose gel electrophoresis. The *-765G→C* and *-1195A→G* genotypes that could be detected were: *765CC* (100 bp fragment), *765GC* (100 + 74 + 26 bp fragments), *765GG* (74 + 26 bp fragments), *1195AA* (273 bp fragment), *1195GA* (273 + 220 + 53 bp fragments) and *1195GG* (220 + 53 bp fragments), respectively.

Statistical analysis

The data analysis was performed using SPSS software

Table 2 Genotype distribution and OR of the *COX-2 -1195A→G* and *-765G→C* polymorphisms in patients with CRC and controls

Genotype	Patients with CRC (*n* = 326)	Controls (*n* = 369)	OR (95% CI)
-1195AA	213 (65.3%)	232 (62.9%)	Reference
-1195GA	101 (31.0%)	124 (33.6%)	0.90 (0.66-1.23)
-1195GG	12 (3.7%)	13 (3.5%)	1.01 (0.45-2.25)
-765GG	241 (73.9%)	249 (67.5%)	Reference
-765GC	75 (23.0%)	112 (30.4%)	0.69 (0.49-0.97)
-765CC	10 (3.1%)	8 (2.2%)	1.29 (0.50-3.33)

OR: Odds ratio; CI: Confidence interval.

(Version 14.0, SPSS, Chicago, IL, USA). Logistic regression was used to assess the association between the genotypes and the risk of CRC. The statistical significance of the *-1195A→G* and *-765G→C* genotype distributions between the patient and control groups was determined by Chi-square analysis. A *P*-value of < 0.05 was used as the criterion of statistical significance and all analyses were adjusted for age and sex. A test for deviation from the Hardy-Weinberg equilibrium, by comparing the expected to observed genotype frequencies, was used. Odds ratios (ORs) and 95% confidence intervals (CI) were calculated. Based on the two polymorphisms tested, a haplotype analysis was performed. In the two populations studied, seven different haplotypes could be distinguished: *AC/AC, AG/AC, AG/AG, GC/AC, GG/AC, GG/AG* and *GG/GG*. The localization of the tumor, distal or proximal, was also included in the database analyses.

RESULTS

Using cancer-free controls as a reference we tested for an association of the two *COX-2* polymorphisms with CRC. The genotype distributions in patients and controls of the two *COX-2* polymorphisms investigated are summarized in Table 2. The observed genotype distributions for the *-765G→C* and *-1195A→G* polymorphisms in patients with CRC and controls were in accordance with the Hardy-Weinberg equilibrium, with *P*-values of 0.19 and 0.99 for patients with CRC and 0.24 and 0.46 for controls, respectively. When both polymorphisms were investigated separately, there was no significant difference in the *-765G→C* or *-1195A→G* allele frequency between the patient and control group. However, the *-765GG* genotype was more frequent in patients than in controls (OR, 1.45; 95% CI, 1.03-2.04). There was no significant difference in the genotype distribution of the *-1195A→G* polymorphism among patients and controls.

Next, the potential association of genotype distribution of the two *COX-2* polymorphisms with tumor localization was investigated. We distinguished proximal and distal tumor localization. Proximal included the cecum, colon ascendens and colon transversum and distal included the rectum, sigmoid, colon descendens and flexura lienalis. No association between the *-765G→C* and *-1195A→G* polymorphisms and tumor localization was detected.

Table 3 *COX-2* haplotypes in patients with CRC and controls

Haplotype	Patients with CRC (*n* = 326)	Controls (*n* = 369)	OR (95% CI)
AC/AC	9 (2.8%)	8 (2.2%)	1.16 (0.40-3.42)
AG/AC	59 (18.1%)	74 (20.1%)	0.83 (0.54-1.27)
AG/AG	145 (44.5%)	150 (40.7%)	Reference
GC/AC	1 (0.3%)	-	-
GG/AC	16 (4.9%)	38 (10.3%)	0.44 (0.22-0.85)
GG/AG	84 (25.8%)	86 (23.3%)	1.01 (0.68-1.50)
GG/GG	12 (3.7%)	13 (3.5%)	0.92 (0.38-2.24)

Also no association of the genotype distribution of the *-765G→C* and *-1195A→G* polymorphisms in the patient group was found with gender and age.

Based on the two polymorphisms tested, a haplotype analysis was performed in the two populations studied and seven haplotypes could be distinguished (Table 3). A significant difference between the *COX-2* haplotypes was observed. The *GG/AC* haplotype was less frequent in patients (OR, 0.44; 95% CI, 0.22-0.85). When the *AC*, *AG* and *GG* haplotypes were investigated separately; the *AC* haplotype tended to occur less frequently in patients than in controls ($OR_{(AG/AC)}$ 0.78; 95% CI, 0.57-1.06).

DISCUSSION

The COX-2 protein was detected in 70% of all colorectal cancer tissues. In adjacent normal colorectal tissue in the same slide the COX-2 protein was not observed. These results suggest that increased expression of COX-2 is associated with CRC[12]. SNPs in the *COX-2* promoter may alter the enzyme activity of COX-2 by differential regulation of COX-2 expression, which may influence the risk of the development of CRC[7-9]. It has been recently demonstrated that the polymorphisms *-765G→C* and *-1195A→G* may have a functional effect on COX-2 expression and enzyme activity[7-9]. Both the *-765G→C* and *-1195A→G* polymorphisms were shown to display a lower *COX-2* promoter activity, which may result in a lower expression of the COX-2 enzyme[5,13].

We investigated the potential association of the *COX-2* polymorphisms *-765G→C* and *-1195A→G* and the risk of developing CRC, and found that the *-765GG* genotype was present more often in patients than in controls. As demonstrated by Zhang *et al*[5] the reporter gene expression driven by the *-765G*-containing *COX-2* promoter was higher as compared to the *-765C*-containing counterpart. This indeed could mean a higher COX-2 expression in *-765GG* individuals.

A study in American Caucasians reported a reduced risk of colorectal adenomas in individuals bearing the *-765GG* genotype, but this lower risk was found only among users of non-steroidal antiinflammatory drugs (NSAIDs). In addition, a lower risk of adenoma among *-765CC* genotypes was found only in non-users of NSAIDs[11]. Zhang *et al*[5] and Tan *et al*[9] reported that the *-765GC* genotype was associated with an increased

risk of esophageal squamous cell carcinoma (ESCC) and CRC, in Chinese populations. The findings of Tan *et al*[9] and Zhang *et al*[5] seem in contrast with our results, since we found a reduced risk of CRC with the *-765GC* genotype. However, racial differences in the study populations may explain these apparent contradictory results, since the distribution of the *COX-2* polymorphisms studied here differs considerably between the Chinese and Dutch study populations. The genotype frequencies found in our Dutch patients with CRC for the *-765G→C* and *-1195A→G* polymorphisms were: 73.9% *GG*, 23.0% *GC*, 3.1% *CC* and 65.3% *AA*, 31.0% *GA*, 3.7% *GG*, respectively. Zhang *et al*[5] in a Chinese population reported genotype frequencies of 90.6% *GG*, 9.4% *GC*, 0% *CC* and 30.5% *AA*, 52.9% *GA* and 16.6% *GG*. Tan *et al*[9] in Chinese patients with CRC recently reported approximately the same genotype frequencies as Zhang *et al*[5]: 91.6% *GG*, 8.4% *GC*, 0% *CC* and 34.5% *AA*, 49.4% *GA* and 16.1% *GG*. These findings suggest that ethnic differences in genotype frequencies of *COX-2* polymorphisms may have a significantly different modulating effect on disease phenotypes in different ethnic populations.

According to Zhang *et al*[5] and Tan *et al*[9] in a Chinese population, the *-1195GA* and *-1195AA* genotypes were associated with an increased risk of ESCC and CRC, respectively. This again is not in line with our findings, since we could not demonstrate a significant difference in the allele distribution of the *-1195A→G* polymorphism between our Dutch patients with CRC and controls.

We also investigated the potential association of the genotype distributions of the *-1195A→G* and *-765G→C* polymorphisms with tumor localization. No association between the two polymorphisms and tumor localization was found, which is in accordance with the results of Tan *et al*[9] who found a very similar distribution of both *COX-2* genotypes in patients with colon (n = 403) or rectal (n = 597) cancer.

The *COX-2 GG/AC* haplotype (*-1195G-765G/-1195A-765C)* was found to be present less frequently in patients. When the *AC*, *AG* and *GG* haplotypes were investigated separately, the *AC* haplotype tended to be less frequently present in patients with CRC than in controls ($OR_{(AG/AC)}$ 0.78; 95% CI, 0.57-1.06). This is in line with the findings of Zhang *et al*[5] who demonstrated that the luciferase expression of the *AG* constructs was higher than the expression of the *AC* constructs, suggesting that the *AC* haplotype was associated with a lower COX-2 expression and a decreased risk of CRC.

However, Zhang *et al*[5], Tan *et al*[9] and Moons *et al*[14] found an association of the *AC* haplotype with an increased risk of ESCC, CRC and esophageal adenocarcinoma (EAC). These findings are in contrast with our results, as described above. In addition, the predicted expression levels of the COX-2 protein are higher in *AG* versus *AC* haplotype individuals, according to Zhang *et al*[5], which is not in agreement with the hypothesis that high expression of COX-2 is a risk factor for colorectal or esophageal carcinoma. It should be noted however that haplotype frequencies of *AC* are very low in the patient and control populations studied by Zhang *et al*[5] and Tan *et al*[9], being 4.5% *vs* 1.6% and 3.8% *vs* 1.8%, respectively, compared to 21.2% *vs* 32.6% in our study. In the study of Moons *et al*[14] the *AC* haplotype occurred in 25.0% of the total study population, who were patients with esophageal adenocarcinoma, Barrett's esophagus and reflux esophagitis, a proportion which is very close to our data. In the study of Moons *et al*[14] unfortunately no cancer-free controls were included, but patients with Barrett's esophagus or reflux esophagitis were used as controls, both of which would confer a risk of esophageal adenocarcinoma.

In summary, we found a significant difference in the *-765G→C* polymorphism distribution between the patients with CRC and the control group; the *-765GG* genotype was associated with an increased risk for CRC. The *GG/AC* haplotype was found less frequently in patients with CRC and may be associated with a reduced risk of CRC. These findings suggest a modulating role for the *COX-2* polymorphisms *-1195A→G* and *-765G→C* in the development of CRC in a Dutch population.

COMMENTS

Background

Cyclooxygenase-2 (COX-2) is a key enzyme in the development and progression of neoplasms. COX-2 was found to be over-expressed in gastrointestinal tumors, including those of the colon/rectum. The corresponding *COX-2* gene is polymorphic and two single nucleotide polymorphisms (SNPs; *-1195A→G* and *-765G→C*) were demonstrated to influence the expression of COX-2. Therefore, these polymorphisms may modulate the risk for gastrointestinal cancers, such as cancers of the colon/rectum.

Research frontiers

In this study, the *-765GG* genotype was associated with an increased risk of developing CRC and the *GG/AC* haplotype seemed to protect against CRC.

Innovations and breakthroughs

The *COX-2* polymorphisms *-765G→C* and *-1195A→G* may modulate the development of CRC in a Dutch population.

Applications

Screening for the *COX-2 -765GG* genotype in a population at risk of colorectal cancer may be valuable in future in order to select the high risk patients. Information and prevention programs can than be focused on these patients.

Terminology

COX-2 is an enzyme that catalyzes the conversion of arachidonic acid in prostaglandin H2, the precursor of other prostaglandins, prostacyclin and thromboxanes. These regulatory compounds play a role in many biological processes such as cell proliferation, angiogenesis, immune function and inflammation, which are all crucial in the development and progression of neoplasms.

Peer review

The manuscript, reported by Hoff *et al*, analyzes COX-2 polymorphisms *-765G→C* and *-1195A→G* and colorectal cancer (CRC) risk in a Dutch population. This manuscript contributes in the effort to characterize some molecular signatures as risk factors for colon cancer in different ethnic populations.

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S- Editor Tian L **L- Editor** Cant MR **E- Editor** Ma WH