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The Association Of G>C -765 Promoter Polymorphism Of Cox-2 Gene With Colorectal Cancer: A Case Study In Dr. Moh. Hoesin General Hospital, Palembang, Indonesia

M. Alsen Arlan[1], Ahmat Umar[2], Sarup Singh[3], Efman Manawan[4], Irsan Saleh[5]

[1,2,3,4]Digestive Surgery Department, Medical Faculty, Sriwijaya University, Palembang / Moh Hoesin General Hospital, Palembang, Indonesia
[5] Biomedical/Statistics Department, Faculty of Medicine, University of Sriwijaya, Palembang, Indonesia
aslenusri@gmail.com

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Abstract:
Colorectal cancer (CRC) is a common malignancy in the gastrointestinal tract which ranks fourth among all cancers worldwide. Polymorphism is a mutation in a gene in a population with a frequency greater than 1%. The impact of this polymorphism is a change in the vulnerability of a population towards a disease.
To analyse the relationship between G>C polymorphism in promoter -765 of COX 2 gene and the risk of contracting colorectal cancer in Asian population living in Palembang, South Sumatera Indonesia.
Analytical observational study with a comparative study approach (case control) to obtain associationship of known allele polymorphism of COX-2 gene variant at Promoter -765 G > C with incidences of CRC cases. The association was analysed using chi-square test and fisher's exact test between the genotype mutant type (CC and GC) compared to normal wild-type genotype (GG) in both case and control groups.
By using the wild type GG genotype as a comparison, the statistical results showed no significant difference in the proportion of colorectal cancer cases in homozygous CC mutants and wildtype GG genotype with the p value of 0.1145. The similar finding was also found in heteroxygous mutant GC genotype where there was no significant correlation of the gene variant with the incidence of colorectal cancer found in this study (p = 1.00).
Genotype polymorphism (CC and GC) at-765 promoter of COX-2 gene was not significantly associated with the incidence of colorectal cancer in population living in Palembang, Indonesia.
Keywords: *Polymorphism, Colorectal cancer, COX-2, -765 promoter, cyclooxygenase*

INTRODUCTION

Colorectal cancer (CRC) is the fourth most common cases worldwide where about 10 million new cases reported annually[1]. The incident of CRC in the USA is more common in women with 10.1% percentage as compared to only 9.4% in men. However, the occurrence of this disease is not equally distributed in all around the world which the number of CRC cases is higher in western countries as compared to other part of the world[1]. Thus, the differences of the number of the cases might attributed to different genetic background of the patients. In Indonesia, the Ministry of Health reported the incident of CRC cases is about 19.1 for men and 15.6 for women per 100 000 populations[2].

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Despite the higher number, the incident rate is much lower due to its high population of 232 million. The cases reported in Indonesia is mainly sporadic and largely associated with young patients with hereditary familial background [3,4]. Hence, uncovering the genetic cause which lead to the disease of will provide a useful data for targeted treatments and populations. There were two types of cyclooxygenase enzymes namely COX-1 and COX-2 transcribed from COX-1 and COX-2 gene respectively which were responsible for the formation of prostaglandins. The role of prostaglandins in inflammation is widely researched and the construction of nonsteroidal anti-inflammatory drugs (NSAIDs) is on the basis of inhibiting the action of this enzyme[5]. The expression of COX-2 gene is low in normal tissues and the increment of its expression is due to its pro-inflammatory and monogenic nature. The high expression of COX-2 is closely related to the cancer development which attributed to inflammation, angiogenesis, immunity system and cell proliferation processes [6-10]. Polymorphism is a gene mutation which occurrence affects more than 1% of the population. Both wild type (normal) and mutant alleles occur in a population despite causing disease or not. However, the vulnerability of a population towards a disease is highly dependent on the gene polymorphism. Study conducted by Holf et tube containing anti- coagulant ethylene diamine tetra acid (EDTA) for DNA extraction and polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) to analyse the gene polymorphism in the patients. The bivariate analysis was then conducted by checking the normality of the COX-2 polymorphism data distribution and the occurrence of the CRC.

RESULTS AND DISCUSSION

al., (2009) suggested that single nucleotide polymorphism (SNP) in COX-2 promoter -765 will change the function of COX-2 enzymes through different regulation of COX-2 expression and disturb its enzyme-regulation process [10].

To this date, there is no research conducted on the influence of the promoter -765 G > C on COX-2 gene towards the risk of contracting colorectal cancer in Indonesia. Thus, the results of this study will add into the literature on underlying genetic background which might affect the rate of contracting CRC representing small population in Indonesia.

METHODOLOGY

The study population involved in this study comprised of all CRC patients sought treatment at Dr. Moh. Hoesin General Hospital, Palembang Indonesia. 40 samples were chosen for CRC group (case) and healthy individuals (control) group. In each group, 21 people were male and 19 were women. The independent variable in this research was the variant polymorphism allele G > C -765 promoter in the COX-2 gene and the dependent variable is the occurrence of colorectal cancer. The data was obtained from medical records as well as blood sample results. 3ml of blood samples from the participants in the study were drawn into a The data on G>C SNP polymorphism of -765 promoter in COX-2 gene and the incidence of colorectal cancer was analysed using chi-square test and fisher's exact test to find the associationship between mutant type genotypes (CC and GC) and normal wild type genotype (GG), also between mutant alleles (C) and normal allele (G) in both groups. The results obtained were tabulated in Table 1 below.

Table 1. The relationship of G>C -765 promoter polymorphism of COX-2 gene with colorectal cancer cases

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Polymorphism	Group			*p*	Colorectal Cancer Risk	
	Case n (%)	Control n (%)	Total n (%)		OR	95% CI
Genotype:						
CC	4 (10)	0	4 (5)	0.1145	9.831	0.5089-189.9
GC	4 (10)	5 (12.5)	9 (11.25)	1.00	0.8750	0.2158-3.548
GG	32 (80)	35 (87.5)	67 (83.75)		-	
Total	40 (50)	40 (50)	80 (100)			

fisher's exact test, OR = Odds ratio, CI = Confidence interval

By using the wild type GG genotype as a comparator, there was no significant differences in the risk of contracting colorectal cancer in homozygous mutant CC as compared to the GG wildtype genotypes with the p value of 0.1145 (OR =9.831; 95% CI= 0.5089-189.90). The result was also similar with heterozygous mutant GC genotype where no significant association was found between the polymorphism and colorectal cancer cases. The results from 80 samples indicated that both type of promoter in COX-2 gene reduced the production of cyclooxygenase enzyme and in turn disrupting the inflammation process. For most cases, the irregularity of inflammatory response would result in the formation of cancerous cells [11,12,13]. Despite being associated with cancer, there were also research revealing the beneficial effect of functional -765 G/C polymorphism of COX-2 gene. De Vries et al., (2010) found that polymorphism of the gene promoter significantly reduced the risk of Crohn's disease development. The research however only conducted in Dutch population and variations might occur in different population with different genetic background[14]. There was no significant association can be found to link G>C -765 promoter polymorphism of COX-2 gene with the incidence of colorectal cancer cases in Indonesian population living in Palembang. However, it is worth to note that no homozygous CC genotype was found in the control group despite non significant difference of the whole value with the control group. Thus, further research involving larger samples collected from different parts of Indonesia could be conducted to uncover the genetic background leading to colorectal cancer in whole Indonesian population. The results would be a great value in administrating and governing cancer-associated healthcare in Indonesia.

genotypic polymorphism, homozygous and heterozygous mutant were not a significant contributor towards the occurence of colorectal cancer cases in Palembang, Indonesia. The association between COX-2 gene and colorectal cancer was made due to its abnormal activity in cancerous cells as compared to the normal and healthy tissues. A single change of nucleotide which in this case is the change of guanine to cytocine of -765

CONCLUSION

The G>C promoter-765 polymorphism of the COX2 gene was not significantly associated with the occurence of colorectal cancer in Indonesian population living in Palembang. This study provides an additional evidence that the association of COX-2 gene polymorphism with the incident of colorectal

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cancer is still inconsistent and population-dependent.

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