BSM1 POLYMORPHISM ASSOCIATION IN VITAMIN D RECEPTOR

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BSM1 POLYMORPHISM ASSOCIATION IN VITAMIN D RECEPTOR GENES WITH THE OCCURRENCE OF COLORECTAL CANCER IN PALEMBANG, INDONESIA

印度尼西亚帕兰邦维生素D受体基因中BSM1多态性与大肠癌发生的关系

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Abstract

This paper analyzed the association between Bsm1 polymorphism in vitamin D receptor genes with colorectal cancer patients in Palembang, Indonesia. This case control study was conducted from June 2019 to December 2019. The genotype was analyzed using polymerase chain reaction-restriction fragment length polymorphism with the Bsm1 restriction enzyme. Findings showed the distribution of BB-Bb-bb genotype among colorectal cancer patients was 18.6%:26.7%:4.7%, whereas the distribution in a control group was 0%:43%:7%. The distribution of B and b alleles in colorectal cancer patients was 32%:18% compared to the control group's distribution of 21.5%:28.5%. A statistical analysis of Fisher's exact test was conducted to examine the association of polymorphism with colorectal cancer occurrence. Findings demonstrated that there is a significant association was found between Bsm1 polymorphism of vitamin D receptor genes and colorectal cancer occurrences among patients in Palembang, Indonesia. Detailed analysis revealed that rs1544410 in the genotype BB might be a causal factor for colon cancer occurrence. Allele B on the other hand was reported to be the protective factor against colon cancer.

Keywords: Vitamin D Receptor, Gene Polymorphism, Genotype, Allele, Colorectal Cancer

摘要 本文分析了印度尼西亚巨港癌症患者维生素 D 受体基因身材 1 多态性与结直肠癌患者之间的关系。该病例对照研究于 2019 年 6 月至 2019 年 12 月进行。使用身材 1 限制酶和聚合酶链反应-限制性片段长度多态性分析基因型。结果显示，BB-Bb-bb 基因型在大肠癌患者中的分布为 18.6%：26.7%：4.7%，而对照组中的分布为 0%：43%：7%。大肠癌患者中 B 和 b 等位基因的分布为

32%：18%，而对照组为 21.5%：28.5%。进行了费舍尔精确检验的统计分析，以检查多态性与结直肠癌发生的关系。研究结果表明，在印度尼西亚巨港的患者中，维生素 D 受体基因的身材 1 多态性与大肠癌的发生之间存在显着关联。详细分析显示，基因型 BB 中的rs1544410 可能是结肠癌发生的原因。另一方面，等位基因乙是抵抗结肠癌的保护因子。

关键词：维生素 D 受体，基因多态性，基因型，等位基因，结直肠癌

I. INTRODUCTION

Colorectal cancer (CRC) is among the most common causes of death in the United States and the third most prevalent disease in the world [1]. Research from Wahidin et al. [2], Sasmithae et al. [3], and Abdullah et al. [4] stated that Indonesia, despite having no definitive measure of CRC incidence, has experienced an increase in the number of cases reported in 2018 (total cancer cases = 348,809; total cancer death = 207,210). CRC is among the 10 most common types of cancer in the country [2]. According to data from Indonesia Ministry of Health, CRC prevalence was estimated at 1.8 per 100,000 people [2].

A number of studies have attempted to offer a means of helping those with CDC. Newmark [5] and Giovannucci [6] pointed out the value of diet in treating CDC occurrence decades before it became a concern. For instance, according to Giovannucci [6], Lamprecht et al. [7], and Peterlik et al. [8], CRC risk may be reduced with vitamin D, which forms long chains of bile and fatty acids in the small intestine to protect colon epithelial cells from various mutagens. Vitamin D also contributes towards the processes of cell proliferation, cell differentiation, apoptosis, angiogenesis, and cell cycle regulation [16].

The vitamin D receptor (VDR) gene is located at the chromosome 12q13 locus and plays a vital role in vitamin D metabolism. This includes calcium absorption in the intestine, bone metabolism, and the differentiation and proliferation of immune cells and carcinogenesis, which cover differentiation, proliferation, apoptosis, and cell cycle regulation processes [7], [8], [9], [10]. The prominence of this gene does not logically connect to complications disrupting its normal function. It might cause some complication that would amends its operation and disrupt its normal function.

Polymorphism is a gene mutation that occurs as both wild-type (normal) alleles and mutant alleles in more than 1% of a population [17]. However, the allele frequency may vary between healthy and sick populations. Polymorphism affects the susceptibility of a population to contracting a disease and can vary with population ethnicity, as similar races and cultures may have different polymorphism compared to other ethnicities [17]. Bsm1 polymorphism (rs1544410) in VDR genes occurs at intron 8 with allele pairings of BB, Bb, and bb, affecting the regulatory stability of mRNA. Polymorphism at this location will ultimately cause VDR mRNA degradation and influence receptor density [11].

II. METHODOLOGY

The sample contained 86 volunteers divided evenly into experimental and control groups. The experimental group consisted of CRC patients, while the control group comprised clinically healthy individuals (observational area residents and health workers from Palembang district) not diagnosed with CRC based on colonoscopy examination. The CRC patients and the control participants involved in this study were required to meet the participation criteria. It should be noted that a person can suffer from an affliction without being diagnosed as having it. Samples were taken using a consecutive sampling technique (CRC patients who met the participation criteria were placed in experimental group samples until the determined number of total samples was reached). In this study, three parameters tested are BB, Bb and bb, indicating that the minimum number of participants are 30. Data were analyzed using SPSS 16.0 for Windows [15] to determine the distribution and frequency of genotypes and VDR gene alleles in both groups. The relationship between Bsm1 polymorphism VDR genes and CRC incidence was analyzed using two-by-two table analysis to produce an odds ratio (OR) calculation with a 95% confidence interval (CI).

The average participant ages for the experimental and control groups were 45.93 ± 13.56 years and 50.65 ± 13.73 years, respectively. The experimental group population had 11 participants (25.6%) suffering from colon cancer and 32 participants (74.4%) with rectal cancer. In this study, no participants had both cancers simultaneously.

All participants underwent DNA isolation and polymerase chain reaction-restriction fragment

length polymorphism processes, the distribution and frequency of the rs1544410 VDR gene was tabulated. In order to, measure the association of rs1544410 in VDR genes with genotype BB, Fisher's exact test was utilized.

III. FINDINGS

As mentioned in the methodological section, after all participants underwent DNA isolation and polymerase chain reaction-restriction fragment length polymorphism processes, the distribution and frequency of the rs1544410 VDR gene was tabulated (Table 1).

Table 1.
The distribution of the genotype frequency of VDR rs1544410 in all research samples

Group			
Genotype	**Experimental (n, %)**	**Control (n, %)**	**Total (n, %)**
BB	16 (37.2)	0 (0)	16 (18.6)
Bb	23 (53.49)	37 (86.0)	60 (69.7)
bb	4 (9.3)	6 (14.0)	10 (11.7)
Total	43 (100)	43 (50)	86 (100)

Table 1 indicates no participants were found to possess genotype BB in the control group, while 16 participants (37.2%) in the experimental group carried this genotype. The distribution and frequency of the B and b alleles in rs1544410 were then tabulated (Table 2).

Table 2.
The distribution of allele frequency of Bsm 1 polymorphism in VDR rs 1544410 gene on experimental group (n=86)

Group			
Genotype	**Experimental**	**Control**	**Total**
	(n, %)	**(n, %)**	**(n, %)**
B	55 (32%)	37 (21.5%)	92 (53.5%)
b	31 (18%)	49 (28.5%)	80 (46.5%)
Total	86 (50%)	86 (50%)	172 (100%)

Results indicate that 32% of the experimental group participants had higher allele B frequency, whereas 21.5% was reported for the control group. The genotype distributions of BB, Bb, and bb and the distributions of allele B and b among CRC patients, based on age groups, are reported respectively as follows:

Table 3.
Polymorphism of Bsm1 according to the age group

Polymorphism		**Group age**		**Total**
		Age < 50 (n, %)	**Age > 50 (n, %)**	
Genotype	BB	9 (20.9)	7 (16.2)	16 (37.2)
	Bb	14 (32.6)	9 (20.9)	23 (53.5)
	bb	2 (4.7)	2 (4.7)	4 (9.3)
Total		25 (58.2)	18 (41.8)	43 (100)
Allele	B	32 (37.2)	23 (26.8)	55 (64)
	b	18 (20.9)	13 (15.1)	31 (36)
Total		50 (58.1)	36 (41.9)	86 (100)

The association of polymorphism with CRC occurrence was analyzed using Fisher's exact test to obtain an OR of 2.1 (95% CI = 1.8–4.39; p = 0.001). The association of rs1544410 in VDR genes with genotype BB was also determined using Fisher's exact test. The results indicated that rs1544410 in the genotype BB might be a causal factor for colon cancer occurrence (OR = 2.03; 95% CI = 0.256–5.949; p = 0.013). Allele B on the other hand was reported to be the protective factor against colon cancer (p=0,004; OR=0, 22 and 95%CI=0.075-0.657).

Table 4.
Analysis of genotype BB of Bsm 1 polymorphism on VDR gene with the occurrence of colorectal cancer

Group				**CRC risk**		
Polymorphism	**Experimental (n, %)**	**Control (n, %)**	**Total (n, %)**	***p***	**OR**	**95%CI**
Genotype						
BB	16 (37.2)	0 (0)	16 (18.6)	0.001	2.1	1.8-4.39
Bb	23 (53.5)	37 (86.0)	60 (69.8)	0.744	1.84	0.6-2.85
bb	4 (9.3)	6 (14.0)	10 (11.6)	As comparison		
Total	43 (100)	43 (100)	86 (100)			

Table 5.
Analysis of the association of Allele B with the colorectal cancer

Group				**CRC risk**		
Polymorphism	**Experimental (n, %)**	**Control (n, %)**	**Total (n, %)**	***p***	**OR**	**95%CI**
Allele						
B	55 (32)	37 (21.5)	92 (53.5)	0.006	0.42	0.231-0.786
b	31 (18)	49 (28.5)	80 (46.5)			
Total	86 (50)	86 (50)	172 (100)	As comparison		

IV. Discussion

In this research, the relationship analysis between the polymorphism as a variable and the occurrence of colorectal cancer are nominal data, and hence the association was analyzed using Fisher's exact test to determine any non-random association. Based on the data obtained, the distribution of allele B frequency in the experimental group is 53.5%, and the frequency of allele b is reported at 46.5%. The statistical analysis reported that there is a significant association between allele B and colorectal cancer.

Several other studies have reported the same results, as excellently reviewed by Köstner et al. [12]. On the other hand, Bai et al. [13] and Jenab et al. [14] found the opposite, reporting that the polymorphism of the genotype BB in Bsm1 of the VDR rs1544410 gene lowered the risk of CRC.13,14 Despite having contradictory results, it is worth noting that different study populations were involved in each study. This might lead to the conclusion that the association of Bsm1 might be population-specific and highly dependent on ethnicity and genetic background.

V. Conclusion

The result of this study reveals a clear causal relationship between the Bsm1 polymorphism in the VDR (rs1544410) and colon cancer occurrence among CRC patients in Palembang, Indonesia. However, the contrasting findings by Bai et al. [13] and Jenab et al. [14] call for more research to be conducted to obtain a clearer overview of the causal relationship between polymorphism and CRC cases. It is speculated that the geographical location of the population plays a vital role in determining the association of allele polymorphism and CRC, which might bring insight into genomic differences and adaptabilities in different populations around the world. It should be noted that all the participants involved in this study were from Palembang Indonesia.

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