

Smokers with a Duration of >20 Years are at a 3.7 Times Higher Risk and White Cigarette Users are at a 2.4 Times Higher Risk for the Occurrence of Colorectal Cancer at Prof. Dr. I.G.N.G Ngoerah Hospital

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ABSTRACT

Background: Colorectal cancer is one of malignancy that occurs in the colon and rectum. In Indonesia, the number of colorectal cancer patients according to the Indonesian Ministry of Health in 2018 was 15,985 cases in men and 11,787 cases in women. Smoking habits have been established as a risk factor for colorectal cancer. Smoking duration, type of cigarette, and number of cigarettes specifically pose a risk factor for colorectal cancer. This study aims to prove the highest risk factor for the incidence of colorectal cancer as assessed by multivariate testing at the Prof. dr. I.G.N.G. Ngoerah General Hospital. **Method:** This research is an observational case control study in determining the difference between smokers of white cigarettes and clove cigarettes with a smoking duration of more than 20 years and more than 20 cigarettes per day which are risk factors for colorectal cancer. This research was conducted at Prof. dr. I.G.N.G. Ngoerah General Hospital Denpasar from February 2022 – August 2022. The sample for this study were all Digestive Surgery patients who came for treatment at Prof. dr. I.G.N.G. Ngoerah General Hospital with colorectal disease based on inclusion exclusion criteria. The statistical tests used were univariate, bivariate analysis with the Chi Squared Test and multivariate with multiple logistic regression. **Result:** Smokers with a duration of more than 20 years ($p=0.001$), number of cigarettes more than 20 cigarettes per day ($p=0.014$), and types of white cigarettes ($p=0.008$) are risk factors for colorectal cancer based on bivariate analysis. **Conclusion:** Smoking duration >20 years is the highest risk factor for colorectal cancer with an increased risk of 3.7 times higher than smoking duration <20 years.

Keywords: colorectal cancer; duration of smoking; number of cigarettes; types of smoking; risk factors

INTRODUCTION

Colorectal cancer is the second most common cancer in women and the third most common in men worldwide. It is a malignant disease that occurs in the colon and rectum. This disease is often challenging to detect early, as in the early stages, colorectal cancer is mostly asymptomatic. Symptoms of colorectal cancer typically manifest in advanced stages, after patients experience obstructive ileus or palpable lumps in the abdomen. Some patients only seek medical attention after metastasis to the liver or lungs has occurred.

A total of 1.9 million new cases were reported in 2020 [1], and this figure is estimated to increase by 60% to reach 2.2 million new cases by 2030. In developed countries, the risk of colorectal cancer is significantly higher in men compared to women (6.4%:5%). Meanwhile, in developing countries, the incidence of colorectal cancer is substantially increasing. This rise appears to reflect changes in physical activity and diet. The projected new cases in the United States in 2017 were approximately 135,430, representing 8% of all cancer types.

In Europe, there were about 450,000 new cases of colorectal cancer in 2017. Countries and regions with Western lifestyle habits (North America, Europe, Australia, and New Zealand) have the highest incidence of colorectal cancer, while the lowest incidence is found in Africa and Asia. In Indonesia, the number of colorectal cancer patients according to the Ministry of Health of the Republic of Indonesia in 2018 was 15,985 cases in males and 11,787 cases in females [2,3,4].

Smoking habits have been identified as a risk factor for colorectal cancer for the past 10 years. In the United States, the prevalence of smoking has varied between men and women over the past 20 years. In 1996, Giovannucci hypothesized that smoking initiates carcinogenesis in colorectal tissues, with tumors emerging 30-40 years after the onset of smoking habits. A study conducted by T Gram and colleagues in 2020 in Los Angeles revealed that male smokers had a 39% higher risk of developing left-sided colon cancer, while women had a 20% higher risk of right-sided colon cancer. In Indonesia, based on research conducted by Hartono and colleagues in 2019 at the Presidential Hospital RSPAD Gatot Soebroto, it was found that 54.2% of colorectal cancer patients had a smoking habit. Bivariate analysis using the Chi-Square test indicated a significant relationship between smoking and the occurrence of colorectal cancer. According to a study by Jenses et al. in 2012, a smoking history of more than 20 years can increase the risk of colorectal cancer by 20% [5,6].

Conventional cigarette smoke contains carcinogenic substances such as Polycyclic Aromatic Hydrocarbons (PAHs), Aromatic Amines, Nitrosamines, and Heterocyclic Amines (HCAs). In contrast, vape or electronic cigarette smoke mostly consists of nicotine. These substances enter the digestive system or the bloodstream and can induce epigenetic changes in the KRAS and BRAF genes [7]. Generally, there are two types of cigarettes: white cigarettes and kretek cigarettes. More than 90% of Indonesian smokers use kretek cigarettes. The difference between the two types lies in their composition. Kretek cigarettes contain higher levels of Tar and Nicotine (about three times more), but on the flip side, kretek cigarettes contain cloves. Cloves contain eugenol, known for its pro-apoptotic and anti-cancer properties in colorectal cancer by targeting BCL-2. According to a study by Petrocelli in 2020, 800 mcg of eugenol can induce apoptosis after 72 hours in colorectal cancer epithelial cells. However, to date, there has been no research comparing the risk magnitude between smokers of white and kretek cigarettes for the occurrence of colorectal cancer [8,9].

The degree of smoking also determines the risk of colorectal cancer. According to the World Health Organization (WHO), there are three degrees of smoking (light, moderate, and heavy) based on the number of cigarettes consumed per day. According to a study by Akter et al. in 2020, light smokers (1-10 cigarettes) had a Hazard Ratio of 1.18, while moderate smokers (10-20 cigarettes/day) and heavy

smokers had a Hazard Ratio of 1.22 for colorectal cancer. According to a study by Tsoi et al. in 2009, smoking 20 packs/year (2 cigarettes/day) had an Odds Ratio of 1.85, and smoking >40 packs/year (>4 cigarettes/day) had an Odds Ratio of 1.94 for colorectal cancer. In Indonesia, there is currently no research on the risk of colorectal cancer based on the degree of smoking [10,11].

Due to the high incidence and mortality rates of colorectal cancer associated with smoking habits, and the lack of research analyzing the differences in cigarette types concerning the magnitude of colorectal cancer risk, the author is interested in analyzing the differences in the risk magnitude of colorectal cancer between white and kretek cigarette smokers. Additionally, the author is also interested in analyzing the degree, type, and duration of smoking as factors in the occurrence of colorectal cancer at Prof. dr. I.G.N.G. Ngoerah General Hospital in Denpasar, Bali.

METHODS

This study is an observational case-control study aimed at determining the differences between white cigarette and kretek cigarette smokers with a smoking duration of more than 20 years and more than 20 sticks per day, which are risk factors for colorectal cancer. The case group comprises white and kretek cigarette smokers who have colorectal cancer, while the control group consists of white and kretek cigarette smokers who do not have colorectal cancer. The research is conducted at Prof. dr. I.G.N.G. Ngoerah General Hospital in Denpasar, specifically in the Digestive Surgery Clinic, Surgical Triage, and inpatient rooms. The study is scheduled to take place from February 2022 to August 2022.

The target population for this research includes all Digestive Surgery patients seeking treatment at Prof. dr. I.G.N.G. Ngoerah General Hospital for colorectal diseases. The accessible population in this study includes all Digestive Surgery patients with colorectal cancer and those without cancer, who have a smoking habit. Sampling is done using consecutive sampling techniques, meaning samples are taken based on inclusion and exclusion criteria. Inclusion criteria for the case and control groups include all Digestive Surgery patients diagnosed with colorectal cancer who smoke white and kretek cigarettes, with complete clinical data recorded in medical records. Exclusion criteria for the case and control groups include patients with cancers other than colorectal, those with incomplete clinical data, those with a history of alcohol consumption, and those with a family history of colorectal cancer. The minimum total sample size for this study is 98 patients.

Data collection is directly obtained from its source using primary data in the form of a questionnaire containing information on demographic data, characteristics, and variables of the samples under investigation. Independent variables consist of the duration of smoking white and kretek cigarettes, the number of cigarettes smoked per day for white and

kretek cigarettes, and the type of cigarette. The dependent variable is the occurrence of colorectal cancer.

Univariate analysis aims to describe the characteristics of subjects and research variables based on colorectal cancer and non-cancer groups. Numeric ratio data variables are presented with mean and standard deviation, while categorical scale variables are presented with relative frequencies. Descriptive statistical analysis is presented using cross-tabulation tables to assess the comparability of subjects between colorectal cancer and non-cancer groups.

Bivariate analysis with the Chi-Squared Test is conducted to determine the differences in duration and the number of cigarettes smoked per day for white and kretek cigarette smokers, as well as the significance of the type of cigarette in the occurrence of colorectal cancer.

To assess the risk magnitude, Odds Ratios are calculated using case-control risk estimation, with precision expressed as a 95% confidence interval (CI), and a significance level set at $P < 0.05$. Multivariate analysis is performed to identify the most significant variables influencing the occurrence of colorectal cancer using Multiple Logistic Regression. The entire data analysis process is carried out with the assistance of the Statistical Programs for Social Science (SPSS) version 30.

RESULTS

This research involved 98 samples derived from patients suffering from colorectal cancer and those without colorectal cancer in the Digestive Surgery Department of Prof Dr. I G.N.G. Ngoerah General Hospital. The characteristics of the samples were described based on age, gender, body weight, height, body mass index (BMI), nutritional status, and dietary patterns.

TABEL 1: Characteristics of the Research Sample.

Characteristic	Colorectal Cancer Diagnosis	
	Colorectal cancer (n=49)	Without Colorectal cancer (n=49)
Age (year) (mean, SD)	55 ± 11.8	47 ± 13.7
Gender		
Male	26 (53.1%)	29 (59.2%)
Female	23 (46.9%)	20 (4.8%)
Body Mass Index (kg/m²) (mean, SD)	21 ± 3.3	22 ± 3.1
Nutritional Status (n, %)		
Abnormal	12 (24.5%)	16 (32.7%)
Normal	37 (75.5%)	33 (67.3%)
Diet (n, %)		
Lack of fiber	21 (42.9%)	31 (63.3%)
Enough fiber	28 (57.1%)	18 (36.7%)

Based on Table 1, the mean age of patients with colorectal cancer was 47 years ($SD \pm 13.7$), while those without colorectal cancer had a mean age of 55 years ($SD \pm 11.8$). Males were the predominant gender in this study, both among patients with colorectal cancer, comprising 26 patients (53.1%), and patients without colorectal cancer, comprising 29 patients (59.2%). The body mass index (BMI) for patients with colorectal cancer was found to have a mean of 21 kg/m² ($SD \pm 3.3$), while for those without colorectal cancer, it was 22 kg/m² ($SD \pm 3.1$).

Normal nutritional status was the most prevalent category in this study, both among patients with colorectal cancer, with 37 patients (75.5%), and patients without colorectal cancer, with 33 patients (67.3%). Dietary patterns differed significantly between the two groups; the majority of patients with colorectal cancer had an adequate fiber intake, with 28 patients (57.1%), while the majority of patients without colorectal cancer had insufficient fiber intake, with 31 patients (63.3%).

TABLE 2: Hypothesis Testing Between Variable.

Variables	Diagnosis of Colorectal Cancer		OR (CI 95%)	p
	Colorectal cancer (n=49)	Without colorectal cancer (n=49)		
Smoking duration				
>20 years	34 (66.7%)	17 (33.3%)	4.3 (1.8-9.9)	0.001*
<20 years	15 (31.9%)	32 (68.1%)		
Number of Cigarettes				
>20 cigarettes	26 (65.0%)	14 (35.0%)	2.8 (1.2-6.5)	0.014*
<20 cigarettes	23 (39.7%)	35 (60.3%)		
Type of Cigarettes				
'White' cigarettes	29 (64.4%)	16 (35.6%)	3.0 (1.3-6.8)	0.008*
Kreteks	20 (37.7%)	33 (62.3%)		

*: p<0,05 (significant).

According to Table 2, there is a statistically significant difference (p<0.05) between the occurrence of colorectal cancer and smoking duration, the number of cigarettes, and the type of cigarettes when tested bivariate. Smoking for >20 years increases the risk of colorectal cancer by 4.3 times compared to smoking for <20 years.

According to the statistics, patients with a habit of smoking more than 20 cigarettes are at a 2.8 times higher risk of developing colorectal cancer compared to patients who smoke fewer than 20 cigarettes. Additionally, the type of cigarette, specifically white cigarettes, significantly increases the risk of colorectal cancer by threefold compared to kretek cigarettes.

TABLE 3: Multivariate Candidate Model Selection.

Variables	Sig	Exp (B)	95% CI for Exp(B)	
			Lower	Upper
Smoking duration	0.001*	4.267	1.832	9.939
Number of Cig.	0.015*	2.826	1.225	6.520
Type of Cig.	0.009*	2.991	1.310	6.826
Gender	0.542	1.283	0.577	2.853
Age	0.045	2.289	1.019	5.142
Nutritional Status	0.372	0.669	0.277	1.618
Fiber intake	0.044	0.435	0.194	0.980

*: p<0.025 (significant), can proceed to the multivariate model.

TABLE 4: Multivariate Analysis.

Variables	Sig	Exp (B)	95% CI for Exp(B)	
			Lower	Upper
Smoking duration	0.017*	3.775	1.268	11.238
Number of Cig.	0.954	0.967	0.310	3.011
Type of Cig	0.040*	2.448	1.101	5.987

*: p<0.05 (significant).

Multivariate analysis using Multiple Logistic Regression (Table 4) reveals that two fixed variables significantly influence the occurrence of colorectal cancer after considering control factors, namely smoking duration ($p=0.017$) and cigarette type ($p=0.04$). It is known that smoking duration has the highest precision of Odd Ratio or Exp(B) with a 95% CI and is the most influential factor in the occurrence of colorectal cancer in this study.

DISCUSSION

The research results indicate differences in age characteristics between patients with and without colorectal cancer. Colorectal cancer can occur in young adults and adolescents, but the majority of cases occur in individuals aged over 50. With the passage of time, it is estimated that there will be an increase in the incidence of colorectal cancer in the population under 50 in the next 10 years, making early detection crucial at a young age [12]. Being diagnosed at a young age (<50 years) is associated with advanced stages and a higher incidence of colorectal cancer recurrence, but survival rates are assessed similarly when compared to older patients [13].

Based on gender, it was found that males are more likely to experience colorectal cancer in this study. Colorectal cancer predominantly occurs more frequently in men. Both men and women are at risk of colon cancer, but men are twice as likely to develop rectal cancer [14]. Various studies with specific gender analyses indicate that women tend to be safer from the risk of colorectal cancer compared to men. These findings suggestively indicate the protective role of the sex steroid hormone estrogen in preventing the development of colorectal cancer. Key proliferative pathways in colorectal cancer tumorigenesis show sexual dimorphism, providing better survival in women through estrogen-regulated genes and cell signaling. Estrogen regulates the activity of the Kv channel family (KCNQ1:KCNE3), which controls the fundamental ion transport function of the large intestine and the epithelial-mesenchymal transition through two-way interaction (Wnt/ β -catenin signaling pathway). Estrogen also modulates the proliferative response of colorectal cancer in hypoxia through estrogen receptor signaling (GPER), HIF1A, and VEGF [15].

The research results showed an average BMI of 21.6 kg/m², and nutritional status tended to be normal among Indonesian subjects. These findings differ slightly from research that found most newly diagnosed colorectal cancer patients tended to have abnormal nutritional status with an average BMI of 27.1 kg/m². This is because the subjects involved in the research have different characteristics [16]. Obesity, defined as a BMI of around 30 kg/m², especially at a young age, is a risk factor for colorectal cancer. BMI at the initiation of first-line chemotherapy is not associated with patient outcomes after chemotherapy. Weight loss is associated with higher stages and an increased risk of patient death as the disease progresses.

Meta-analysis studies show the strongest relationship between nutritional status measured by BMI and colorectal cancer compared to weight, height, or waist circumference, indicating an 8% increased risk for every 5 kg/m² increase in BMI [17].

The research findings indicate differences in fiber intake based on the characteristics of patients with and without colorectal cancer. Dietary fiber has been associated with a decreased risk of colorectal cancer. However, it is still unclear at which stage and in which carcinogenic pathway fiber can act against the development of colorectal cancer [18]. Researchers who found a significant correlation between fiber intake and the incidence of colorectal cancer speculate that the consumed fiber will influence the diversity of microbiota in the intestines and ultimately prevent the formation of cancer. Others argue that consumed fiber can affect gene signaling processes at the cellular level and influence the occurrence of colorectal cancer [19].

Research findings indicate that based on the characteristics of fiber intake, there are differences in fiber intake between patients with and without colorectal cancer. Dietary fiber has been associated with a reduction in the risk of colorectal cancer. However, as of now, it is still unclear at which stage and in which carcinogenic pathway fiber can act against the development of colorectal cancer [18]. Researchers who found a significant correlation between fiber intake and the incidence of colorectal cancer speculate that the consumed fiber will influence the diversity of microbiota in the intestines and ultimately prevent the formation of cancer. Some also argue that consumed fiber can affect gene signaling processes at the cellular level and influence the occurrence of colorectal cancer [19].

Bivariate analysis indicates that smoking duration has an impact on the occurrence of colorectal cancer. This finding aligns with the study by Hannan et al., 2009, which shows that an increased smoking duration appears to be associated with an increased risk of colorectal cancer ($p = 0.005$), with the strongest relationship between smoking duration and colorectal cancer observed among those who have smoked for 20 years or more. This finding also supports the hypothesis by Giovannucci, stating that two to four decades of follow-up may be necessary to detect early occurrences of colorectal cancer due to the effects of smoking on the early stages of colorectal carcinogenesis [20].

Smoking is considered one of the highly important risk factors for colorectal cancer. Cigarettes are known to contain numerous carcinogens and genotoxic agents. Cancer arises from the complex interaction of genetic vulnerability and environmental factors. The longer the exposure to these agents, the higher the risk of cells dividing abnormally into cancerous formations. Research by Murphy found a positive association between smoking and colorectal cancer in former smokers but not for current smoking history [21].

Colorectal cancer can arise from one or a combination of three different mechanisms: chromosomal instability (CIN), CpG island methylator phenotype (CIMP), and microsatellite instability (MSI). Longer smoking duration is associated with findings of high MSI indicators, positive CIMP, and positive BRAF mutation subtype [22]. Induction of epigenetic changes in KRAS and BRAF genes can occur when a significant amount of cigarette smoke containing carcinogenic substances enters the digestive tract or the bloodstream over a chronic or multi-year period [8,23].

In addition to the duration of smoking, cases of colorectal cancer are also associated with the quantity of cigarettes. A study by health experts on men aged 35-40 years indicates a twofold increased risk in men who have smoked at least 10 packs of cigarettes per year. The study's findings consistently show that individuals who smoke 1-2 packs (20-40 cigarettes) per day or accumulate 20-40 packs of cigarettes per year have a risk about 2-3 times higher than smokers with fewer amounts, and a fivefold higher risk compared to non-smokers [24]. A recent meta-analysis examined the correlation between smoking history and molecular pathways in sporadic colorectal cancer, where smoking >20 packs is more associated with right-sided colon cancer. Right-sided colon cancer is associated with more aggressive disease and a worse prognosis than left-sided colon cancer [23].

In this study, the type of cigarette also influences the occurrence of colorectal cancer. Two types of cigarettes were compared in this study: white cigarettes and kretek cigarettes. These two types of cigarettes differ in their content, with kretek cigarettes containing higher levels of tar and nicotine. More than 90% of Indonesian smokers use kretek cigarettes, which contain more tar and nicotine than conventional cigarettes. There are natural compounds found in high concentrations in clove tips, which is the differentiating active ingredient in kretek cigarettes compared to conventional cigarettes, namely eugenol. Eugenol is a pungent spice component that has anticancer and pro-apoptotic properties in colorectal cancer by targeting BCL-2. Apoptosis is one of the methods the body uses to eliminate unnecessary or abnormal cells, although cancer cells have strategies to avoid this apoptosis. Eugenol significantly induces changes in metabolic pathways that inhibit cancer by inhibiting tumor suppressor genes APC and p53, as well as oncogene KRAS. The apoptosis-inducing activity of eugenol can circumvent these strategies, leading to apoptosis and causing cancer cell death [8,9,25]. This may be associated with the reduced risk of colorectal cancer in Kretek cigarette smokers compared to conventional cigarette smokers.

Among the many toxic and carcinogenic substances produced from tobacco exposure, tobacco-specific nitrosamines (TSNA) and polycyclic aromatic hydrocarbons (PAH) have been extensively studied in relation to exposure and carcinogenicity.

TSNA is found in native tobacco as well as tobacco smoke and is formed during the preservation and processing of tobacco. TSNA has been found to be more abundant in traditional cigarettes than in other cigarette variants, including smokeless cigarettes. TSNA induces sustained proliferative signaling, evasion of growth suppressors, resistance to cell death, enhanced replication, induction of angiogenesis, activation of invasion and metastasis, reprogramming of energy metabolism, genomic instability, and mutations, evasion of immune damage, promotion of tumor inflammation. The main signaling pathway activated by TSNA that can lead to these characteristics is through β -AR and nAChR signaling [26].

Not only through genetic signaling, but classical cigarette smoke also affects carcinogenesis through the imbalance of gut microbiota. Microbial dysbiosis was observed in mice exposed to cigarette smoke, with significant differences in bacterial species, including an increased abundance of *Eggerthella lenta* and a depletion of *Parabacteroides distasonis* and *Lactobacillus* spp. Metabolomic analysis showed an increase in bile acid metabolites, especially taurodeoxycholic acid (TDCA), in the colon of mice exposed to cigarette smoke. The increased TDCA correlated with enhanced oncogenic MAPK/ERK signaling (mitogen-activated protein kinase/extracellular signal-regulated protein kinase 1/2) and disruption of intestinal barrier function [27].

In addition to the research findings aligning with theories discussed in the literature review, the novelty of this study lies in successfully comparing the risk magnitude in smokers with white and kretek cigarettes in the occurrence of colorectal cancer, an aspect not extensively explored in previous research. These results are expected to serve as a reference for further research, especially regarding the types of cigarettes and colorectal cancer. However, the study has limitations, as it focused only on three risk factors, warranting further research to compare other risk factors. Additionally, there is a tendency for recall bias due to the data collection process through questionnaires, as the ability of patients to recall exposure information may differ between the case and control groups.

CONCLUSION

- (1) Smokers with a duration of more than 20 years are a risk factor for colorectal cancer at Prof. dr. I.G.N.G. Ngoerah Central General Hospital.
- (2) Smokers with a daily cigarette consumption of more than 20 cigarettes are a risk factor for colorectal cancer at Prof. dr. I.G.N.G. Ngoerah Central General Hospital.
- (3) White cigarette smokers are at a higher risk of colorectal cancer compared to kretek cigarette smokers.
- (4) Smoking duration >20 years is the highest risk factor for colorectal cancer incidence, with a 3.7-fold higher risk compared to smoking duration <20 years.

SUGGESTION

- (1) Subsequent research may consider the use of electronic medical records or computerized systems during data collection to facilitate the research implementation and avoid recall bias.
- (2) Future research is expected to consider the analysis of other risk factors or delve deeper into the comparison of cigarette variables based on other characteristics (such as electronic cigarettes, manual clove smoking, and so on).
- (3) Further research is encouraged to focus on investigating eugenol, a substance contained in cloves, as an anti-colorectal cancer agent.

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