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THE EFFECT OF LOW-FIBER DIETS ON COLORECTAL CANCER INCIDENCE IN SOUTHEAST AND EAST ASIA: SYSTEMATIC REVIEW AND META-ANALYSIS

Tia Eka Novianti[1], Qonita Rachmah[1], Merryana Adriani[1]
[1]Department of Nutrition, Faculty of Public Health, Universitas Airlangga, Surabaya, Indonesia
Correspondence address: Tia Eka Novianti
Email: tia.eka.novianti-2016@fkm.unair.ac.id

ABSTRACT

Introduction : Colorectal cancer is a malignant tumor that grows in the colon tissue. In the Asian region, in 2018, cases and deaths from colorectal cancer are highest in East Asia (there were 736,573 cases and 325,128 of them died) and Southeast Asia (there were 95,223 cases and 52,475 of them died). **Aims:** Several studies have been conducted regarding the effect of a low-fiber diet and an increased risk of colorectal cancer, but it still shows mixed results. **Methods:** This study is an unobstrutive study with a systematic review and meta-analysis method. Data sources came from 14 primary studies with a case-control study design that met the inclusion criteria. Data analysis was performed using CMA software trial version 3.0 with a confidence level of $\alpha = 5\%$. Research with low-fiber diet variables shows heterogeneous variations in results so that the chosen model is random effect model. **Result:** The analysis states that there was a significant relationship between a low-fiber diet (CI: 0.421–0.867) and an increased risk of colorectal cancer due to the role of soluble and insoluble fiber. Lack of intake of soluble fiber can decrease insulin action and blood sugar control or the production of short-chain fatty acids, whereas insufficient intake of insoluble fiber can increase the potential for interactions between mutagens and colonic mucosa. **Conclusion:** The results of the study are expected to be an input for a proper diet so that there is no increase in cases of colorectal cancer.

Keywords: colorectal cancer, low-fiber diet, meta-analysis, systematic review

INTRODUCTION

Globally, cancer is the second leading cause of death after cardiovascular disease (Ministry of Health Republic of Indonesia, 2015). In recent years, cancer has become a chronic disease that has a high incidence. In 2012, new cases of cancer reached 18.1 million and 8.2 million of them died. Then in 2018, cancer deaths increased to 9.6 million (World Health Organization, 2018). Basic Health Research (Riskesdas) in 2018, shows that the prevalence of cancer / tumors is 1.8 per 1000 population. This prevalence increased from the 2013 Riskesdas data, which amounted to 1.4 per 1000 population, or around 347,792 people (Ministry of Health Republic of Indonesia, 2018). By 2030, the incidence of cancer is estimated to reach 21.7 million people and 13 million of them will die. Cancer will increase in incidence in poor and developing countries (American Cancer Society, 2014).

The World Health Organization (2020) states that in 2018 there were 348,809 cancer cases in Indonesia, with 207,210 of them dying. There are three types of cancer with the highest incidence in Indonesia for all genders, namely breast cancer, cervical cancer and colorectal cancer. In the Asian region, cases and deaths due to colorectal cancer in 2018, mostly occurred in East Asia (there were 736,573 cases and 325,128 of them died), then Southeast Asia (there were 95,223 cases and 52,475 of them died), and then Central Asia - South and West Asia (World Health Organization, 2018).

Colorectal cancer is a malignancy of the colon tissue, which consists of the colon and / or rectum (American Cancer Society, 2014). Dietary history is one of the factors that can increase the risk of this

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type of cancer (Rahmadania et al., 2016). Diet habits with a low fiber consumption pattern are thought to increase the risk of colorectal cancer (Chen et al., 2015). Research by Afrah and Makhmudi (2013) states that the daily fiber intake of the Indonesian population is still low, which is around 10.5 g / day.

Indonesian Cancer Foundation (2017) states that the main problem in cancer prevention is a lack of knowledge about cancer in the community and a lack of public awareness in implementing healthy living behaviors to reduce cancer risk and early detection of cancer. As a result, most cancers are found at an advanced stage and are difficult to treat, thus placing a huge burden on cancer patients and their families.

Research on the causes and risk factors for colorectal cancer related to diet showed different results between each study. However, there are also those showing the same research results. For example, 7 out of 14 studies stated that low fiber intake was a risk factor of colorectal cancer, while the rest showed insignificant results. The difference in the results from various studies regarding risk factors for colorectal cancer related to diet can cause problems, especially in constructing a theory of risk factors for colorectal cancer or making the results of these studies as a basis for decision-making to intervene. Therefore, we need a literature review study that uses a method to summarize several studies with similar discussion topics, so as to produce conclusions.

This study aims to apply a meta-analysis method with an effect size odds ratio in primary studies regarding the effect of a low-fiber diet on an increased risk of colorectal cancer in Southeast and East Asia, so that accurate conclusions can be obtained.

METHODS

This study used a meta-analysis based on research articles on how fiber consumption can as a protective factor in the increased risk of colorectal cancer in Southeast and East Asia region, which was published in 2001 to 2020 in the online publication database of scientific articles PubMed and Google Scholar.

Articles are selected based on inclusion criteria, that is using a case-control study, articles accessible to full-paper, and topics discussed regarding a low-fiber diet that can increase the risk of colorectal cancer. In addition, a critical appraisal is carried out on each article by following the framework of PRISMA (the Preferred Reporting Items for Systematic Review and Meta-Analysis) as shown in Figure 1.

Identification of the articles found was carried out by reviewing the article titles and abstracts, then conducting a full-paper review. Articles are excluded from the analysis if: (a) the subject is irrelevant, (b) is not a case-control study, (c) the information provided in the study results is insufficient for data extraction, (d) the consumption pattern is not a low-fiber diet.

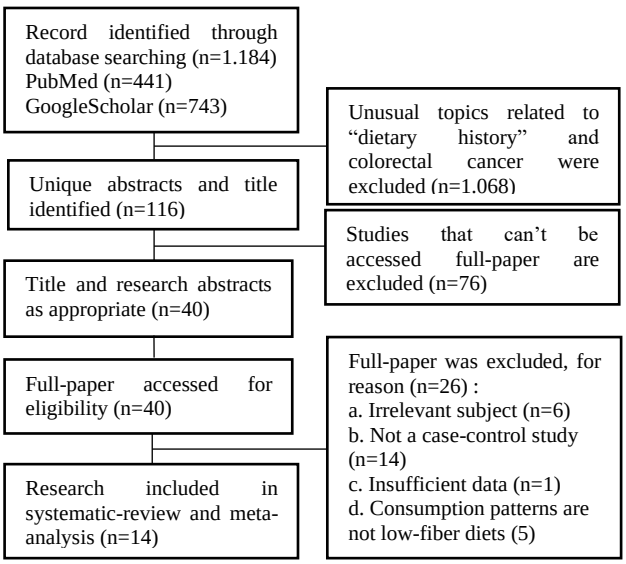

Figure 1. PRISMA flow chart

Random-effect model or fixed-effect model was used to calculate the combined of risk ratio. Data were analyzed using the CMA 3.0 software and presented in the form of a forest plot.. This research has passed the Ethics Commission Faculty

of Public Health, Universitas Airlangga No. 93/EA/KEPK/2020.

RESULT

This study found 14 primary studies with case-control study design that were relevant for meta-analysis (Table 1). The results of a meta-analysis are presented in Figure 2. It shows that there was a significant relationship between a low-fiber diet and an increased risk of developing colorectal cancer (OR = 0.605 [95% CI 0.421 - 0.876]).

Table 1. A Systematic Review of the Effect of Fiber Consumption on the Risk of Colorectal Cancer in Southeast Asia and East Asia

Author, Year	Region	Number of Samples	Type of Fiber	Fiber Intake	Effect Size OR (95% CI)
Swari et al. (2019)	Denpasar-Bali, Indonesia	Case : 52 Control : 52	Total fiber	<21 g/day	6.750 (2.852-15.973)
Hapsari and Murbawani (2016)	Semarang, Indonesia	Case : 18 Control : 18	Total fiber	<25 g/day	0.153 (0.016-1.468)
Ramadas and Kandiah (2010)	Kuala Lumpur, Malaysia	Case : 59 Control : 59	Total fiber	3.93 vs 7.07 g/ day	0.140 (0.049-0.396)
Sriamporn et al. (2007)	Khon Kaen, Thailand	Case : 253 Control : 253	Fiber from vegetable/fruit	198-528 portion/year	1.000 (0.707-1.414)
Song et al. (2015)	Qingdao, Tiongkok	Case : 265 Control : 252	Total fiber	20.52 g/day	0.440 (0.268-0.723)
Uchida et al. (2010)	Fukuoka, Jepang	Case : 816 Control : 815	Total fiber	13.7 vs 13.7 g/day	0.870 (0.579-1.307)
Zhong et al. (2014)	Guangdong, China	Case : 613 Control : 613	Total fiber	9.2 vs 10.5 g/day	0.380 (0.266-0.542)
Wang et al. (2018)	Shandong, China	Case : 317 Control : 317	Total fiber	High/low	0.350 (0.285-0.429)
Chun et al. (2015)	Korea	Case : 150 Control : 116	Total fiber	38 vs 49 g/day	0.220 (0.,083-0.582)
Thohir (2019)	Padang, Indonesia	Case : 34 Control : 34	Fiber from vegetable	<4x/week	0.218 (0.068-0.700)
Ngelangel et al. (2009)	Filiphina	Case : 283 Control : 283	Fiber from vegetable	<1x/week	0.860 (0.493-1.500)
Kim et al. (2003)	Korea	Case : 125 Control : 247	Fiber from vegetable	High/low	0.800 (0.493-1.308)
Poomphakwaen et al. (2014)	Thailand	Case : 230 Control : 230	Fiber from vegetable/fruit	High/low	0.940 (0.623-1.418)
Wakai et al. (2006)	Nagoya, Jepang	Case : 507 Control:2.535	Fiber from fruit	High/low	0.730 (0.501-1.063)

In the quantitative abstraction selection stage, 14 abstraction values were obtained which were sorted through systematic review. Based on the results of the heterogeneity test, the model selection used was the random effect model. This model is used if the heterogeneity test results show the effect size data is heterogeneous.

In addition, it is known that the p-value is 0.006 (p-value <α 5%), which means that the low-fiber diet variable is a factor that can increase colorectal cancer. The p-value combination value is influenced by the p-value of each study. Of the 14 primary studies, it is known that only seven studies showed a p-value <0.05. The summary effect that shows that a low-fiber diet as a factor that can increase of colorectal cancer is found in studies by Ramadas and Kandiah (2010), Zhong et al. (2014), Chun et al. (2015), Song et al. (2015),Wang et al. (2018), Swari et al. (2019) and Thohir (2019). While different results are shown by research conducted by Kim et al. (2003), Wakai et al. (2006), Sriamporn et al. (2007), Ngelangel et al. (2009), Uchida et al. (2010), Poomphakwaen et al. (2014) and Hapsari and Murbawani (2016), .

The summary effect is depicted on the forest plot with the diamond symbol (♦). In the diamond figure, it can be seen that the confidence interval lines of the combined 14 primary studies are narrower than for each primary study indicated by the lines that pass through each primary study square. The narrow confidence interval line on the summary effect indicates that the results of combining 14 primary studies are more accurate than the results of each study.

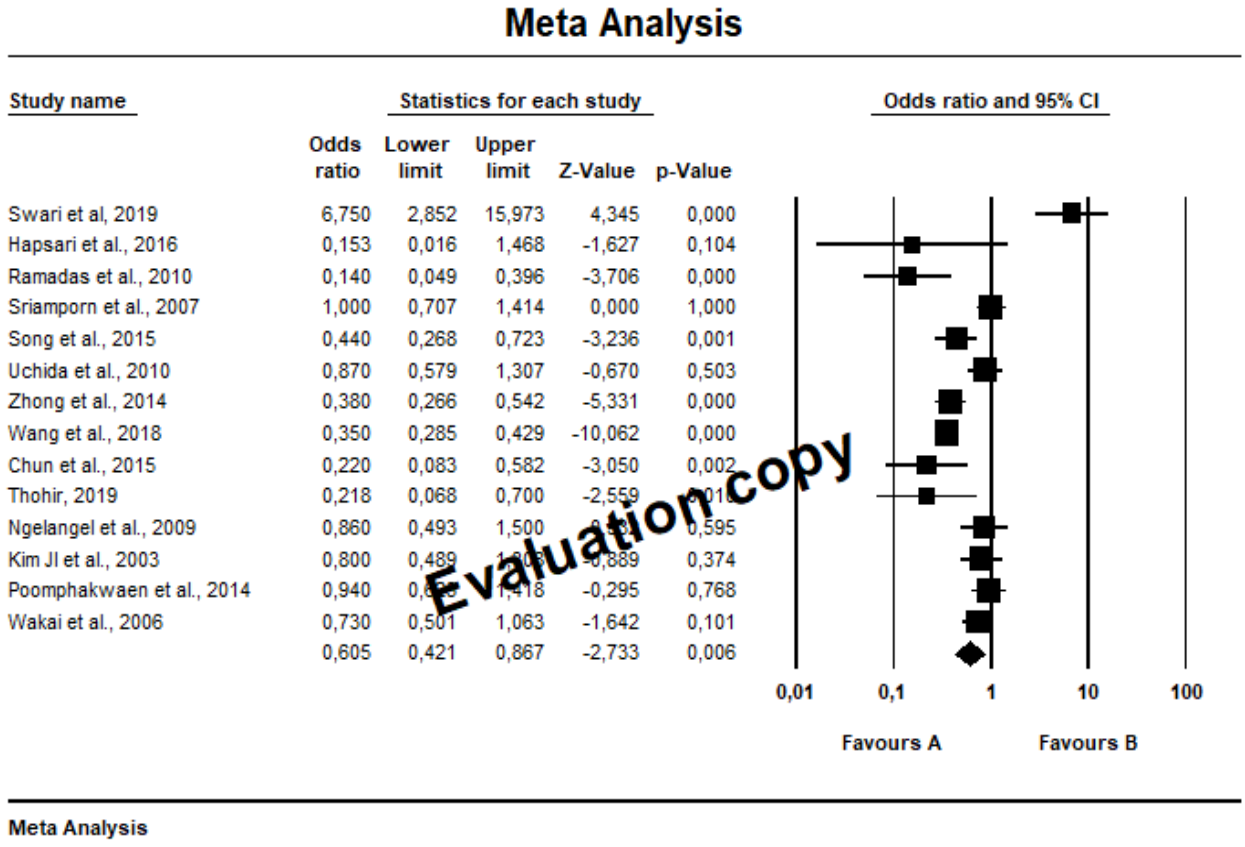

Figure 2. The Forest Plot Meta-Analysis on Low-Fiber Diet Research

DISCUSSION

Colorectal cancer is a malignant tumor that appears in the epithelial tissue of the colon/rectum (Wijaya and Putri, 2013). In 1990, Fearon-Vogelstein introduced the colorectal carcinoma carcinogenesis pathway, called the

adenoma-carcinoma sequence pathway. This pathway begins with the presence of atypical cells, then progresses to mild dysplasia, adenoma hard dysplasia and finally colorectal cancer. In this pathway, APC (adenomatous polyposis coli) mutations occur (Sheridan et al., 2006; Spring et al., 2006 Freeman, 2008). Then in 2003, a new carcinogenesis pathway was discovered by Longacre and Fenoglio-Preiser, called serrated pathways. This pathway is preceded by the presence of a KRAS (Kirsten rat sarcoma viral oncogene homolog) or BRAF (B-Rapidly Accelerated Fibrosarcoma) mutation, with the presence of ACF (Aberrant Crypt Foci) morphological picture. Furthermore, developing into hyperplastic polyps, forming serrated adenoma (SA) and colorectal carcinoma. In the process of carcinogenesis, there is an increase in the number of epithelial cells and decrease in the number of apoptosis, which will then provide a picture of serrated and dysmaturation crypt (Goldstein, 2005; Aust and Barreton, 2010).

Carcinoma is a malignant disease that has multifactorial causes. One of them is the mutation of protooncogens into oncogens (mutant genes). The result of the mutant gene is an oncoprotein, namely Rapidly Accelerated Fibrosarcoma (RAF) (Ziai and Hui, 2012). This gene plays a role in MAPK (Mitogen-Activated Protein Kinase) pathway. In this pathway, RAF has an important role in the processes of cell cycle, starting from proliferation, differentiation, survival to apoptosis (Kolch, 2000; Ducreux et al., 2019). The RAF protein kinase is divided into three, namely A-RAF, B-RAF and C-RAF. Among the three, B-RAF is the gene with the most potential to cause cell proliferation activity (Rahman et al., 2013). Mutations in the B-RAF protein will cause disruption of hydrophobic interactions, which causes the protein to continue to be active and increase the activity of the B-RAF kinase up to 500 times (Ziai and Hui, 2012; Rahman et al., 2013). This occurs because of an obstacle in the process of defosphorylation of GTP to GDP so that the MEK signal pathway on regulation and cell growth continues to be active (Rahman et al., 2013).

In the serrated pathway, it shows impaired Mismatch Repair (MMR), and influences the presence of DNA methylation in the promoter region containing nucleotides (cytosine and guanine) in several tumor suppressor genes. This methylation area is called the CIMP (CpG Island Methylator Phenotype). Disruption in this pathway can lead to genetic instability and eventually tumor formation (Yachida et al., 2009). Several studies suggest that the serrated pathway can develop into colorectal cancer faster than the adenoma-carcinoma sequence (Torlakovic et al., 2008; Aust and Barreton, 2010), which is about eight months (Higuchi and Jass, 2004).

The occurrence of colorectal cancer can be caused by irreversible factors, such as age> 50 years (Mustofa and Kurniawaty, 2013), genetics (Abdullah et al., 2012), history of diabetes mellitus (Yudhani, 2016), ulcerative colitis (Bresalier, 2003), and a history of Chron's disease *(*Thia et al., 2010). In addition, colorectal cancer can also be caused by factors that can actually be changed, such as obesity (Afrah and Makhmudi, 2013), excessive alcohol consumption (Rahdi and Wibowo, 2015), smoking habits (Mustofa and Kurniawaty, 2013), low physical activity (Slattery, 2014), and a history of poor eating habits (Rahmadania et al., 2016).

Dietary history is a detailed retrospective method of dietary assessment to describe foods and / or drinks commonly consumed over a long time period (e.g. 1 month, 6 months, or 1 year). To get quality assessment results, experienced and skilled interviewers are needed (Fegundez et al., 2015). The study design selection in this study is in line with the objective of a case control study, namely to identify risk factors that can cause colorectal cancer.

The high incidence of colorectal cancer in Asia is often associated with poor dietary patterns (Azeem et al., 2015). The influence of the Westernized diet, which generally uses more red meat and processed meat, is low in vegetables and fruit, contributes to an increase in colorectal cases (Yee et al., 2009). The existing Westernized diet in Asia, both in terms of quantity, variety and cooking methods, differing substantially from the Westernized diet in Western countries. This may lead to differences in the body's response to the Asian population to these food components compared to residents of Western countries (Ozaslan et al, 2015).

Dietary fiber is known to be an important component in preventing several diseases. Several studies suggest that a high-fiber diet has a negative relationship with colorectal cancer. Winaktu (2011) states that fiber has different roles in the upper and lower digestive tract which can prevent the developing of colorectal cancer. In the upper digestive tract, fiber has the ability to bind cations by forming cationic bridges. The binding by these fibers is an adsorption mechanism for bile salts, fatty acids and minerals which are carcinogenic. Whereas in the lower digestive tract, fiber serves to provide a substrate for the fermentation process of the intestinal microflora and speed up transit time.

Dietary fiber can be classified based on its solubility, namely fiber that is soluble in water and fiber that is not soluble in water. Fiber components classified as insoluble fiber are cellulose (vegetables), hemicellulose (cereals), and lignin (woody plants). While the fiber components classified as soluble fiber are pectin (fruits, vegetables, beans, potatoes) and gums (nuts, extra seaweed seeds, xanthan).

High soluble fiber intake is known to prevent developing of colorectal cancer. This is attributed to the influence of soluble fiber on insulin and glucose control or short chain fatty acid production. This soluble fiber can slow down the process of glucose absorption from the small intestine, which can reduce hyperinsulinemia (Giacco and Parillo, 2000). Insulin is a growth factor that has a role in cell proliferation and apoptosis, and there is an increased risk of developing colorectal cancer if you have high insulin levels and poor glucose control (Saydah et al., 2003). Soluble fiber can also be converted into short chain fatty acids by bacteria (Sengupta and Tjandra, 2001). In vitro studies have shown that short chain fatty acids (SCFA) are able to inhibit growth and induce differentiation of cancer cells (Gamet et al., 1992).

High consumption of insoluble fiber is known to decrease the developing of colorectal cancer. This is because insoluble fiber can increase the amount of feces, reduce intestinal transit time, and dilute fecal carcinogens, thereby reducing the potential for interactions between mutagens in feces and colonic mucosa (Lipkin et al., 1999).

Based on the image of the forest plot using the random effect model in primary research with a low fiber diet variable (Figure 2), it shows that the square size that interprets the weight of each primary study in producing the summary effect has a different size. The largest square size is owned by a study initiated by Wang et al. (2018), which is 9.22. This shows that the research of Wang et al. (2018) made the largest contribution to

determining the effect size of 14 primary studies with a low-fiber diet variable.

Research by Wang et al. (2018) was conducted in Shandong province, China involving 317 cases and 317 control groups. The case group had similar characteristics based on age and sex and were diagnosed by two gastrointestinal pathologists, while the control group was a healthy population living in the same area as the case group for more than five years. Data collection was carried out by trained interviewers and applied quality control in data collection so that the data obtained were accurate. Wang et al. (2018) also mentioned that people in Shandong province have the habit of consuming foods high in fat and foods that are processed at high temperatures, such as fried foods and grilled meats.

The summary effect of the primary research on low-fiber diet variables using the random effect size, obtained an odds ratio value of 0.605, with a lower level value of 0.421 and an upper level value of 0.867. This odds ratio value shows that someone with a low-fiber diet will have a 0.605 greater risk of developing colorectal cancer than someone who consumes adequate amounts of fiber.

Research by Swari et al. (2019) was conducted in Denpasar-Bali, Indonesia involving 52 cases and 52 control groups. The case group consisted of patients diagnosed with colorectal cancer at Sanglah General Hospital. Data collection was carried out through Sanglah Hospital medical records and outcome data questionnaires based on interview guidelines. Fiber intake is categorized as deficient if the daily intake of fiber is ≤21 g / day.

Research with the same results was also presented by Ramadas and Kandiah (2010). This research was conducted in Kuala Lumpur, Malaysia involving 59 cases and 59 control groups. The included case group was patients who had been diagnosed histologically with polypectomy, did not have polyps with other types (hyperplastic polyps, FAP and HNPCC), and did not suffer from other chronic diseases. Data collection was carried out directly through interviews. Dietary assessment was carried out 3 x 24 hours via recall (1x weekend and 2x weekdays). The dietary assessment was carried out three times because the study subjects came from the group that did not make dietary restrictions so that daily consumption may vary. The food and drink groups are presented in the form of a household size (URT) so that it is easily understood by the subject. From the research results, it was stated that the case group consumed an average of 3.93 ± 2.42 g / day of fiber, while the control group had an average of 7.07 ± 5.34 g / day.

Research conducted by Song et al. (2015) also showed significant results. This research was conducted in Qingdao, China, involving 265 cases and 252 control groups. The case group included were patients with colorectal cancer based on electric colonoscopy and pathology examination, while the control group included was the group that had been adjusted for sex and age with a range of ≤ 3 years with the case group and had no gastrointestinal abnormalities after medical check-ups and no family history. Data collection was carried out directly by trained interviewers. Diet assessments were carried out using the SQ-FFQ with a span of> 1 year before data collection was carried out. In taking diet data, photos of food samples were also provided to make it easier for respondents. Fiber intake was

categorized as high if the daily fiber intake is> 27.6 g / day.

Research with significant results is also presented by Zhong et al. (2014). This research was conducted in Guangdong province, China, involving 613 cases and 613 control groups. The case group included in this study were inpatients at Sun Yat-sen University Hospital who had been diagnosed with colorectal cancer <3 months ago and had lived in Guangdong province for >5 years. Whereas the control group included in the study was hospitalized patients who has no history of cancer with examination <3 months ago, patients lived in Guangdong province for >5 years, and matched the case group based on age (range 5 years) and gender. Data collection was carried out directly by trained interviewers. Dietary assessments were carried out with the FFQ with a time span> 1 year prior to data collection. The food and drink groups were presented in the form of a household size (URT) so that it was easily understood by the subject. In addition, photo samples of food were also used to make it easier for the subject to understand the portion sizes of these foods. The average daily fiber intake of the subjects was 14.92 gr / day (male subjects) and 12.65 gr / day (female subjects).

Research by Chun et al. (2015) also showed significant results. This research was conducted in Korea involving 150 cases and 116 control groups. The case group consisted of patients at Seoul University Hospital, who had just been diagnosed with colorectal cancer in the last <3 months and did not have any other types of cancer or other chronic diseases. The control group included in this study were people who came from healthy populations who were not diagnosed with cancer or other chronic diseases based on the results of medical check-ups in the last <1 year. Data were collected directly by trained nutritionists. Diet assessments were carried out through the FFQ questionnaire developed by KDCA (Korea Disease Control and Prevention) with a time span of >1 year intake data prior to data collection. Fiber intake was categorized as low if the daily intake of fiber is <27.5 g/day.

Research with the same results was also presented by Thohir (2019). This research was conducted in Padang, Indonesia and involved 34 people as control group and 34 people as case group. The case group included in the study were inpatients or outpatients at M. Djamil Padang Central General Hospital who were diagnosed with colorectal cancer in 2019. Meanwhile, the control group was individuals from a healthy population who were not diagnosed with colorectal cancer. Data collection was carried out directly by researchers and assisted by five enumerators who were students of the Faculty of Nursing, Andalas University. Dietary assessments were carried out through the modified Epidemiological Questionnaire for Colorectal Cancer.

The results obtained were in accordance with the theory that states that soluble and insoluble fiber can decrease the developing of colorectal cancer. The presence of soluble fiber can affect insulin action and control blood sugar or bile acid production, while insoluble fiber can reduce the potential for interactions between mutagens and colonic mucosa (by increasing fecal mass and reducing transit time). To minimize the occurrence of colorectal cancer, a person is recommended to consume a minimum of 25 g/day of fiber (both soluble and insoluble fiber), while for someone who

has a family history of cancer, the recommended fiber consumption is 35-40 g/day (Duijnhoven, 2009).

CONCLUSIONS

The summary effect of the primary research shows that low fiber diet is a variable that shows significant results (OR=0.605 [95% CI 0.421 - 0.876]). A low-fiber diet can increase of developing of colorectal cancer due to the role of soluble and insoluble fiber. Lack of intake of soluble fiber can decrease insulin action and blood sugar control or the production of SCFA (Short-Chain Fatty Acids), whereas insufficient intake of insoluble fiber can increase the potential for interactions between mutagens and colonic mucosa.

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