INFLUENCE OF DIET PATTERN ON THE RISK OF COLORECTAL CANCER: A SYSTEMATIC REVIEW

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ABSTRACT

Colorectal cancer ranks fourth most cases in Indonesia. Diet is one of the risk factors for colorectal cancer. The purpose of this study was to determine the effect of diet in increasing the risk of colorectal cancer and its mechanism in the progression of colorectal cancer. The method used is Preferred Reporting Items for Systematic Review Analysis (PRISMA) on the Google Scholar database, PubMed NCBI, and Science Direct. The results of the analysis of 23 articles that meet the criteria show that several food ingredients can increase the risk of colorectal cancer, including fat, fructose, and nitrate. Smoking and drinking alcohol also increases the risk of colorectal cancer. While vitamin D and fiber can reduce the risk of colorectal cancer. Therefore, this understanding is important for doctors and the public to participate in reducing the incidence of colorectal cancer.

Key words: Risk factors, colorectal cancer, diet

INTRODUCTION

Colorectal cancer, also known as colon cancer, is a malignant tumor of epithelial tissue found in the colon and rectum. The colon is one part of the gastrointestinal tract which is located in the proximal part of the large intestine, while the rectum is located in the distal part and above the anus. Based on data from Globocan 2020, colorectal cancer ranks fourth in the most cases in Indonesia. Colorectal cancer in 2020 accounted for 34,189 new cases (8.6%). Cases of colorectal cancer in Indonesia are relatively high, namely 12.8 per 100,000 population in adulthood with a mortality of 9.5% of all cancer cases. Until now, the etiology of colorectal cancer is still unknown, but there are several risk factors for colorectal cancer.

Factors that increase the risk of colorectal cancer can be divided into two groups, namely non-modifiable factors and modifiable factors. Some of the factors that cannot be modified are age, family history, and environmental factors. While some factors that can be modified are diet and nutrition patterns, physical activity and obesity, smoking, and alcohol consumption (Khosama, 2015). *Westernized lifestyle* also increases the risk of colorectal cancer. *Westernized lifestyle* is a westernized lifestyle with a bad diet, which includes consumption of calories and fat that are too high, consumption of foods lacking in fiber, and obesity (Rossi *et al.*, 2018).

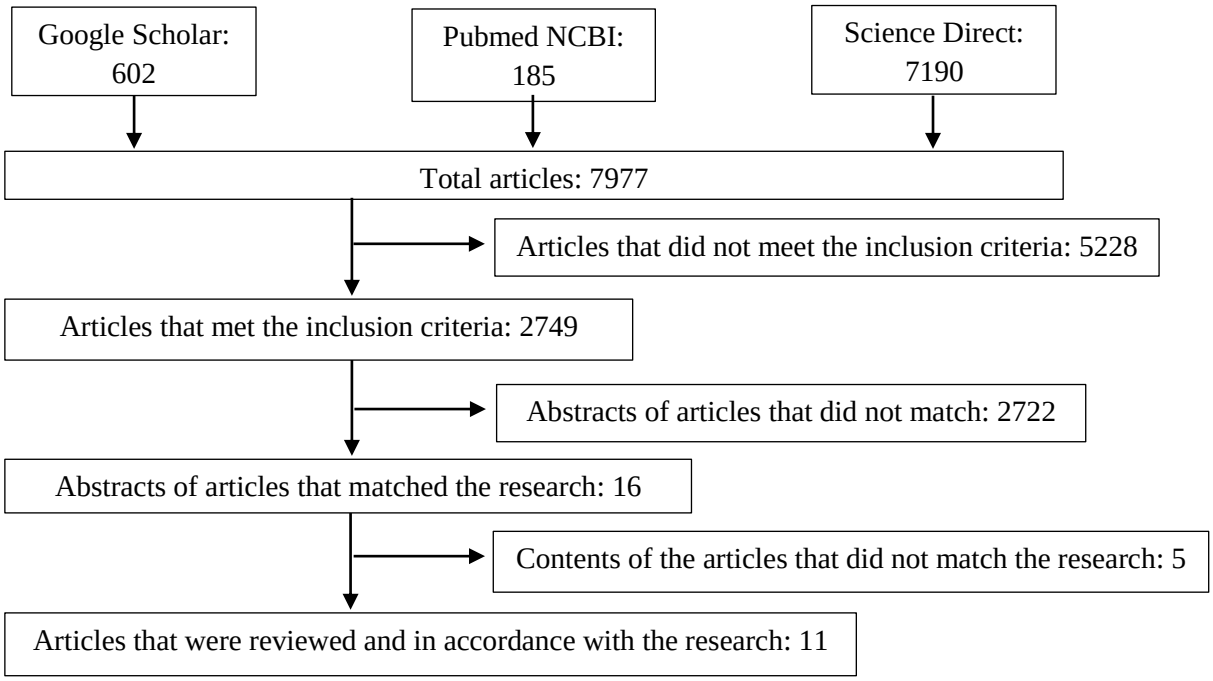
Daily diet has a close relationship with people's lives and also has a relationship with the risk of colorectal cancer. By understanding the risk factors of diet on the incidence of colorectal cancer, it is hoped that it will make it easier for clinicians and the public to carry out appropriate prevention and intervention. Therefore, it is necessary to review and explore the published evidence regarding the relationship between diet and the risk of colorectal cancer.

Based on the description that has been described above, it is necessary to have a review that makes it easier for the public and clinicians to find out more about the basis of the relationship between diet and the risk of colorectal cancer. This article will review the results and evidence of previous studies that have been published and explore 1) the influence of diet in increasing the risk of colorectal cancer, 2) explaining the mechanism of diet in the development and progression of colorectal cancer. Thus, a research article entitled "The Influence of Daily Diet on the Risk of Colorectal Cancer" needs to be written and discussed further.

RESEARCH METHODS

This study used the Preferred Reporting Items for Systematic Review Analysis (PRISMA) method to select articles that met the inclusion criteria. The inclusion criteria in this study were articles discussing the influence of diet on the risk of colorectal cancer, articles from 2012-2022, *original research*, and articles in English and Indonesian. Exclusion criteria in the form of *review articles* and incomplete articles. Searches were made in *databases* Google Scholar, NCBI PubMed, and Science DirectThe first step was identification by visiting the database and writing down the keywords Diet and Colorectal Cancer and a total of 7977 articles were generated. The total articles were then screened and 1749 articles were found that matched the inclusion criteria. The abstract of the article was then read and 27 articles were found that were

in accordance with the research. The last step, the contents of the 27 articles were read and 23 articles were found that were appropriate and have been reviewed



DISCUSSION

Table 1. Effect of Diet on Colorectal Cancer Risk

Literature	Type of food/content	Effect on colorectal cancer
(Rahmadania, Wibowo and Rosida, 2016; Swari, Sueta and Adnyana, 2019)	Fiber	There is a relationship between low fiber consumption and the incidence of colorectal carcinoma
(Woo and Kim , 2013)	Flavonoids	There is no relationship between flavonoid consumption and a reduced risk of colorectal cancer
(Yang and Yu, 2018; Bähr *et al.*, 2022)	Fat	High fat consumption can encourage colorectal tumorigenesis,

(Shen *et al.*, 2022)	Fructose Fructose	consumption Too much can stimulate the development of colorectal cancer.
(Espejo-Herrera *et al.*, 2016)	Nitrates	There is a relationship between nitrate consumption and an increased risk of colorectal cancer.
(Kopp, Vogel and Andersen, 2020)	Vitamin D	Vitamin D is associated with a reduced risk of colorectal cancer.
(Rossi *et al.*, 2018)	Alcohol Alcohol	consumption can increase the risk of colorectal cancer
(Cross and Sinha, 2004)	Smoking Smoking	activity has a relationship in increasing the risk of colorectal cancer
(Alexander *et al.*, 2015)	Red meat	There is no significant relationship between consumption red meat with the risk of colorectal cancer

Mechanism of Diet on Colorectal Cancer Progression

Fiber is a food content that affects the risk of colorectal cancer reduction. In everyday life, fiber consumption can be obtained from fruits, vegetables, and cereals. Fiber consumption and the risk of colorectal cancer have an inverse relationship. Consumption of less fiber can increase the risk of colorectal cancer. Fiber has several ingredients that can prevent colorectal carcinogenesis, namely PUFAs, vitamins, and polyphenols. Fiber in vegetables and fruit can protect the body from colorectal cancer by several mechanisms, namely shortening transit time, forming short-chain fatty acids in the intestine when fermenting dietary fiber, reducing the ability of bile acids to act as carcinogens, and using selenium from cereals which acts as a cofactor. for glutathione peroxidase thereby protecting tissues from oxidative damage (Rahmadania, Wibowo and Rosida, 2016).

Fiber can reduce the concentration of intestinal carcinogens due to increased fecal mass, increased intestinal motility, and increased formation of SCFA during fermentation, especially butyrate, which maintains colonic cell health, increases apoptosis, and inhibits cancer cell proliferation (Yang and Yu, 2018). Butyrate is a major energy source for colonic epithelial cells, a regulator of the proliferation, differentiation, and integrity of the colonocyte barrier, and has a tumor-suppressive effect on the colon. Butyrate also has a role in DNA repair mechanisms by inhibiting the accumulation of carcinogenic DNA (Ocvirk *et al.*, 2019). Fiber dominant diet in

the long term can increase the density of *Firmicutes* and shift the gut microbiota which has an impact on the host immune response that functions as an immunomodulator and anti-inflammatory effect (Jia Yang, 2018). Meanwhile, a low-fiber diet will stimulate the activity of mucus-degrading bacteria, such as *Akkermansia muciniphilia*, which causes a reduced mucus barrier and severe colitis infection (Ocvirk *et al.*, 2019).

Fat has a role in increasing the risk of colorectal cancer. Several studies have shown a strong relationship between fat consumption and an increased risk of developing colorectal cancer. A high-fat diet can stimulate bile acid secretion and cause epithelial regression, colonic mucosal damage, and an increased risk of developing colorectal cancer (Yang and Yu, 2018). Consumption of western foods that are high in fat leads to slower mucus growth and increased penetration of internal mucus. This is related to changes in the composition of the gut microbiota. A high-fat diet can reduce the number of fiber-fermenting bacteria and bacteria of the genus Bifidobacterium. This can lead to a reduced amount of SCFA (short chain fatty acids) and increase the risk of colorectal carcinogenesis (Ocvirk *et al.*, 2019).

High fat intake can stimulate bile synthesis by the liver. The increased amount of bile is then transferred to the large intestine and biotransformed by the gut microbiota. After deconjugation of primary bile acids, conversion is carried out by 7α-dehydroxylation bacteria which increases secondary bile acid products such as DCA (*deoxycholic acid*). The increase in these products will increase the activity of tumor triggers.saturated fat may promote the growth of *Bilophilia wadsworthia*, the gut microbiota that has been linked to colitis and the risk of CRC in humans. Recent studies have also found that fat affects the formation of carcinogenic DNA adducts and triggers the proliferation of *stem cells* and progenitor cells in the colon (Ocvirk *et al.*, 2019).

Fructose has a close relationship with the development of colorectal cancer. Consumption of fructose in everyday life is obtained from sugary drinks and soft drinks. Consumption of fructose can increase the expression of KHK, an enzyme that converts fructose into fructose 1-phosphate. KHK interacts directly with GLUT5 under conditions of excess fructose and lack of glucose. GLUT5 upregulates KHK protein expression by inhibiting lysosomal degradation. Then, *the tumor-promoting function* of GLUT 5 was reversed after *silencing* KHKThis suggests the importance of GLUT5-KHK in mediating fructose-mediated glycolysis in colorectal cancer cell development (Shen *et al.*, 2022).

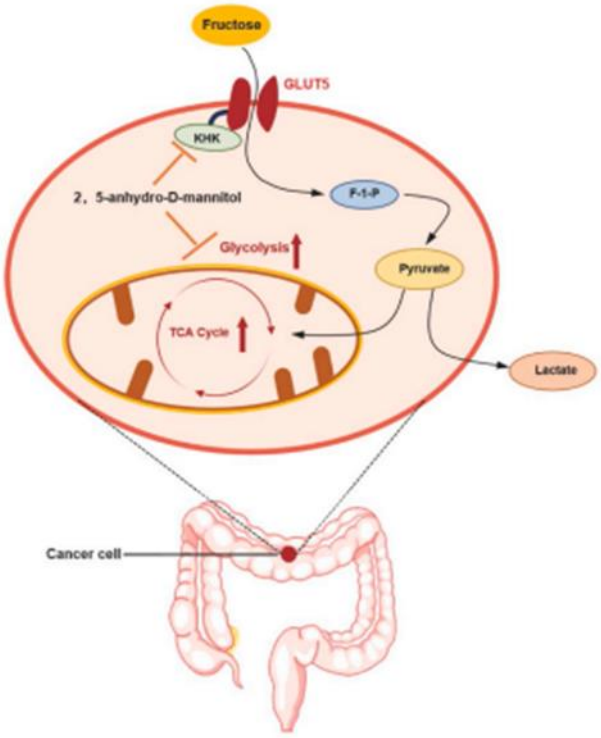


Figure 1. Mechanism of fructose in mediating the development of cancer cells (Shen *et al.*, 2022).

Nitrates have been associated with an increased risk of colorectal cancer. Nitrate consumed will be reduced to nitrite by bacteria in the oral cavity and digestive tract. Ingested nitrite reacts with amines, amides, and other nitrostable compounds to form NOC. Red meat and processed foods are major sources of amines, amides, and hemes that catalyze endogenous nitrosization. This leads to increased NOC formation in feces. Excessive exposure to colonic NOC can cause changes in gene expression that may play a role in the development of colorectal cancer. Consumption of nitrates from processed meats has a major contribution to the development of colorectal cancer (Dellavalle *et al.*, 2014).

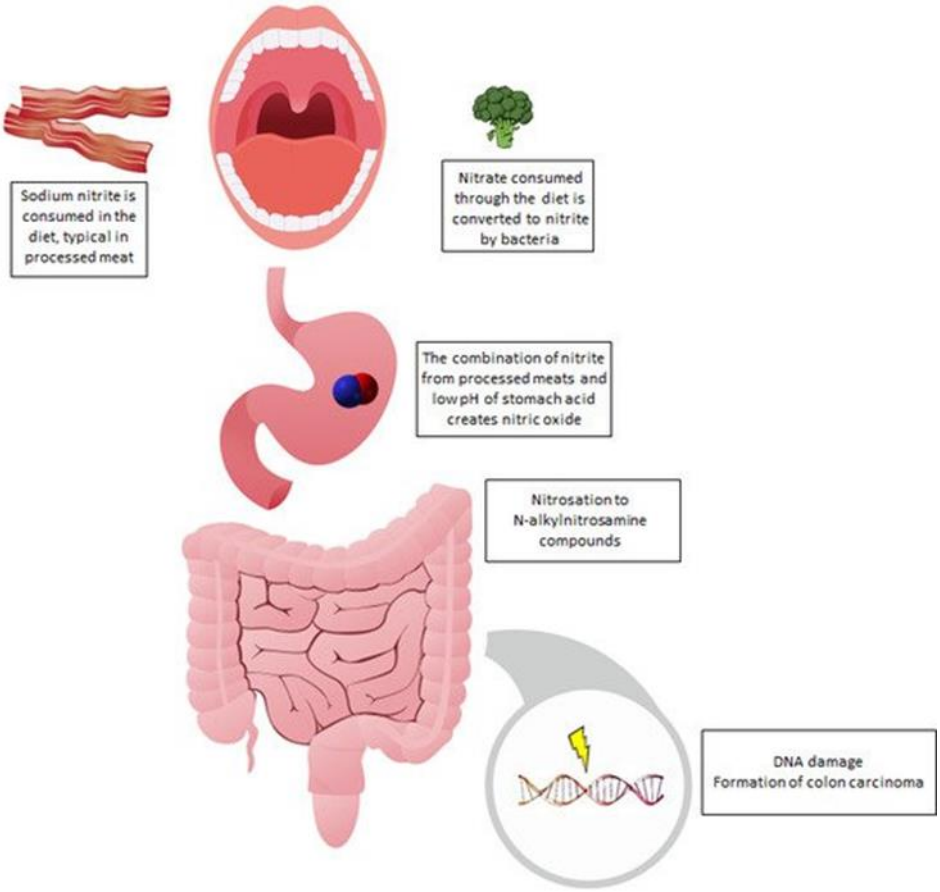


Figure 2. The relationship between nitrate consumption and the development of colorectal cancer (Crowe, Elliott and Green, 2019).

Consumption of high vitamin D can reduce the risk of colorectal cancer and adenoma. In addition, in colorectal cancer patients, consumption and exposure to vitamin D can increase *survival rate*. Vitamin D has an antiproliferative effect by several mechanisms. In Caco-2 cells, calcitriol (a derivative of vitamin D) will increase inhibitors of CDK in the form of CDKN1A and CDKN1B which inhibit CDK2 and CDK6. Inhibition of CDK causes cessation of mitosis in the G1 phase. In addition, vitamin D also activates TGFB1 and sensitizes cells to the *growth inhibitory effect* of TGFB1.

Calcitriol also has some pro-differentiation effects on colorectal cancer cells. Calcitriol increases the activity of alkaline phosphatase in colorectal adenoma cells and colorectal cancer cells. Calcitriol also induces the expression of E-cadherin which causes -catenin to undergo translocation from the nucleus to the E-cadherin complex on the plasma membrane of colorectal cancer cells. It can inhibit cell proliferation and maintain a differentiated phenotype. Calcitriol

has a role in the process of apoptosis of cancer cells. Calcitriol induces apoptosis by increasing the expression of pro-apoptotic proteins such as BAK1 and BAX and decreasing the expression of anti-apoptotic proteins such as BAG1, BCL-2, and BIRC5. Calcitriol also induces *p53-independent apoptosis* and BAK1 protein levels. In addition to the process of apoptosis, calcitriol also has a role in inhibiting angiogenesis. Calcitriol inhibits the elongation of VEGF (vascular endothelial growth factor A) which plays a role in the formation of new blood vessels in tumor or cancer cells. This will then lead to the death of cancer cells or tumors due to a lack of nutrient supply (Dou *et al.*, 2016).

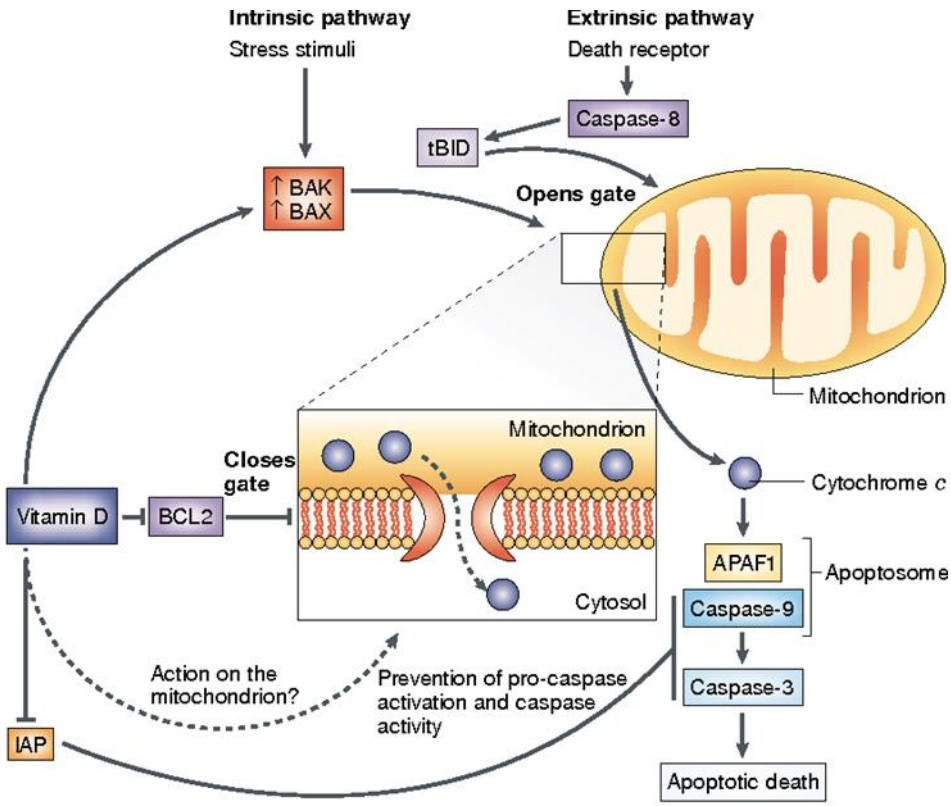


Figure 4 | **Pro-apoptotic actions of vitamin D.** The active form of vitamin D, 1α,25-dihydroxy

Figure 3. Mechanism of vitamin D in inhibiting cancer progression (Lamprecht and Lipkin, 2003).

Alcohol consumption can increase the risk of colorectal cancer. There are several mechanisms by which alcohol induces colorectal carcinogenesis, including influencing genetic abnormalities, epigenetic dysregulation, cell signaling processes, and *microenvironment* tumorEthanol and its metabolites can directly affect stability and genetic expression. Acetaldehyde will bind to deoxynucleotides to form DNA adducts. In addition,

malondialdehyde (MDA) and 4-NHE, a metabolite of ROS, can also form DNA adducts. This causes metabolic processes that increase the formation of ROS that can trigger DNA damage directly and promote colorectal carcinogenesis. Alcohol consumption can also affect DNA indirectly.

Consumption of alcohol continuously (chronic) can lead to malnutrition and vitamin deficiency that affects DNA synthesis and methylation. Ethanol and its metabolites also affect the expression of colorectal cancer genes by altering the levels of miRNAs (microRNAs). These changes can stimulate lipid metabolism, epithelial to mesenchymal transition, angiogenesis, and immune responses. This may play a role in the development of colorectal cancer. Chronic alcohol intake can cause inflammation of the mucosa in the intestines. This is because alcohol can induce microbial dysbiosis and bacterial overgrowth. This leads to LPS exposure in the gut and induces an inflammatory response. This disordered immune response creates *microenvironment* and promotes tumor growth and colorectal carcinogenesis (Rossi *et al.*, 2018).

Smoking has been associated with an increased risk of colorectal cancer. Research shows that nicotine in cigarettes can increase proliferation and decrease apoptosis in vitro (Walter *et al.*, 2014). Cigarettes contain more than 55 carcinogenic agents, including polycyclic aromatic hydrocarbons (PAHs), heterocyclic aromatic amines, and N-nitrosamines. Carcinogenic agents from cigarettes can damage DNA in the colonic epithelium (Binefa *et al.*, 2014). Metabolites from smoking have a role in the risk of developing colorectal cancer. However, not all smokers have cigarette metabolites in their blood. The CYP2A6 gene plays a role in varying degrees of nicotine metabolism. Genetic variations in the nicotinic acetylcholine receptor gene pool also have an influence on circulating cotinine levels in smokers. The metabolite that plays an important role in colorectal carcinogenesis is Hydroxycotinine. Serum hydroxycotinine was identified in individuals who were less efficient at eliminating nicotine metabolites. This causes the individual to have a higher risk (Cross and Sinha, 2004).

CONCLUSION

The increasing incidence of colorectal cancer is a common concern. An unhealthy diet is one of the things that can increase the risk factors for colorectal cancer. Some food ingredients that can increase the risk of colorectal cancer are fat, fructose, and nitrates. Fat can reduce the number of bacteria of the genus Bifidobacterium, bacteria that ferment fiber, thereby causing a lack of

SCFA (short chain fatty acids) that induce colorectal cancer carcinogenesis. Fructose can mediate colorectal cancer carcinogenesis through GLUT5-KHK. Excessive consumption of nitrates can affect gene expression and induce the growth of cancer cells. Smoking habits and drinking alcohol also increase the risk of colorectal cancer. The mechanism of alcohol in inducing the growth of cancer cells can be directly by damaging DNA through excessive ROS production. On the other hand, vitamin D and fiber can lower the risk of colorectal cancer.

Suggestion

Diet is a habit that can be modified. Understanding the relationship between diet and colorectal cancer risk is very important for health workers and the public. By understanding and knowing this, doctors and health workers are expected to provide education for patients and the community. This understanding is also important for the community to adopt a healthier diet and participate in reducing the incidence of colorectal cancer.

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