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The oncologic pathway on colon cancer and correlation with diet: a scoping review

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ABSTRACT

Introduction: The second-leading cause of death worldwide is colon cancer that affects the the gastrointestinal tract. The development of colon cancer therapies frequently uses this signaling pathway as a therapeutic target since oncologic pathways have a significant impact on the incidence. Colon cancer and diet are linked by the Western lifestyle, specifically related to hyperactivity of oncologic pathways.

Method: This scoping review gives information regarding the oncologic pathways and nutrition that involved in colon cancer and has been written following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. The literature search was conducted using the search string main keyword "oncogenic" and "colon cancer".

Results: Nineteen studies were included. The outcomes of interest are induced proliferation, inhibited apoptosis, promoted invasion-metastasis, and angiogenesis. Based on the outcomes of interest, there are several oncologic pathways: WNT/β-catenin, PI3K/AKT, RAS/RAF/MAPK, JAK/STAT, TGF-β, ErbB, NF-kB, HGF/MET, and JNK pathway. Based on the nutrition related to oncologic pathway, there are high intake red meat, high-fat, and low-fiber.

Discussion: Each oncologic pathway has its mechanism, and some have similarities in triggering tumorigenesis. Increased proliferation is due to increased cell cycle activity and decreased tumor suppressor genes. Inhibition of apoptosis is caused by inhibiting caspase activity and pro-apoptotic proteins. Metastasis and angiogenesis are caused due to increased expression of EMT and MMP proteins.

Conclusion: Colon cancer can be affected by certain oncologic pathway with separate mechanism. Besides that, nutrition also affects the hyperactivation of oncologic pathways, thereby increasing the risk of colon cancer.

KEYWORDS

Oncologic pathway; signaling; oncogenic; colon cancer; CRC.

ABBREVIATION LIST

ErbB: Member of Epidermal Growth Factor Receptor.

HGF/MET: Hepatocyte Growth Factor/Mesenchymal Epithelial Transition.

JAK/STAT: Janus Kinase/Signal Transducer and Activator of Transcription.

JNK: Jun N-terminal Kinase.

NF-kB: Nuclear Factor Kappa B.

PI3K/AKT: Phosphatydil-Inositol-3 Kinase/Serin e-Threonine Kinase.

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

RAS/RAF/MAPK: Mitogen-Activated Protein Kinase.

ROS: Reactive Oxygen Species.

SCFA: Short Chain Fatty Acid.

TGF-β: Transforming Growth Factor-β.

WHO: World HealthOrganization.

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INTRODUCTION

The second greatest cause of death worldwide is cancer. A form of cancer known as colon cancer targets the gastrointestinal tract and the colon (large intestine). Colon cancer is the second most prevalent type of cancer overall, accounting for 10% of all cancers in males, and the third most common disease overall in women (9.2% of all cancers in women)[1]. The World Health Organization (WHO) estimates that 1,849,518 instances of colon cancer impact the entire world's population, with a mortality rate of 862,000 individuals[2]. In 2030, there will be 2.2 million new instances of colon cancer worldwide, with a 20% increase in cases[3].

The oncologic mechanisms involved, which cause normal cells to proliferate uncontrollably and prevent apoptosis, have a significant impact on the risk of colon cancer. As a result, the development of colon cancer medications frequently uses oncologic pathways in the disease as therapeutic targets. Each oncologic route has a unique mechanism for affecting the prevalence of colon cancer. Tumorigenesis is impacted differently by each oncologic pathway[4]. One of the challenges in treating colon cancer is the involvement of the oncologic pathway, namely therapy that is off-target or resistant to the oncologic pathways implicated[5].

Colon cancer and diet are linked by compelling epidemiological data. The Western way of life, specifically consuming a high-fat Western diet, has been related to an increase in colon cancer incidence. Consumption of high-fat foods and a diet high in red meat, risk factors for colon cancer, is related to hyperactivity of oncological pathways. Hyperactivity of the oncological pathways involved leads to increased cell proliferation and inhibition of apoptosis[6].

Increased proliferation and apoptotic inhibition are the two main indicators of cancer. Cells that experience unchecked proliferation expand past the number that is considered normal, whereas cells that have apoptosis inhibition experience cell number instability. Colon cancer therapy will be more effective if the right oncologic pathways are targeted because this will assist determine whether the desired therapeutic goal is to limit proliferation or induce apoptosis. Oncology pathways that influence invasion, metastasis, and angiogenesis are should be looked for as a secondary result[7]. Only the two primary oncologic pathways, such as the PI3K/AKT pathway and the WNT/β-catenin pathway, have been extensively studied in relation to colon cancer. Consequently, this review examined the many oncologic pathways and nutrition that connected to colon cancer.

METHODS

This review was carried out based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The inclusion criteria were in vitro studies in the last ten years. The sample population includes colon cancer cellline and human colon cancer tissue. Exclusion criteria were adopted: 1) non-in vitro studies; 2) non-English studies; 3) published in the last ten years. The PECOS framework is used as the basis for inclusion criteria consisting of 1) Problem: colon cancer; 2) Exposure: oncologic pathway; 3) Comparison: no comparison; 4) Outcome: induce proliferation, inhibit apoptosis, invasion-metastasis, and angiogenesis; 5) Study design: in vitro experimental study.

RESULTS

After the literature search, 1.123 studies published in the last ten years were obtained from three databases: PubMed, ScienceDirect, and SpringerLink using boolean operators with the main keyword "oncogenic" and "colon cancer". **Fig 1.** shows searching for studies concerning the oncologic pathway of colon cancer. The number of valid articles included is 19 articles.

Several articles were excluded due to duplication of studies (n=103). There are 879 articles excluded due to topic inconsistency with inclusion criteria, that did not cover the oncologic pathway on colon cancer (n=161). Then, many journals do not ahere to the intended study design so they are excluded such as review articles and books (n=707). Journals that are inaccessible due to subscription also excluded (n=11).

(Table 1) provides an overview of all studies that were a part of this scoping review. The study examined the oncologic pathways involved in the development of colon cancer using a variety of colon cancer cell lines and human colon cancer tissue. The systematic review identified nine oncologic pathways, including WNT/β-catenin, PI3K/AKT/m-TOR, RAS/RAF/MAPK, JAK/STAT, TGF-β, ErbB, NF-kB, HGF/MET, and JNK.

DISCUSSION

Induce Proliferation

Based on the involvement of oncologic pathways in inducing proliferation, there are 8 oncologic pathways involved, namely: 1)WNT/β-catenin; 2) JAK/STAT; 3) ErBb; 4) NF-kB; 5) PI3K/AKT/mTOR; 6) RAS/RAF/MAPK; 7) JNK; and 8) TGF-β. The oncology pathway was described in the 19 articles included[8,9,12-26].

Due to the accumulation of β-catenin brought on by APC mutations, which are involved in the degradation of β-catenin, the WNT/β-catenin pathway stimulates proliferation in colon cancer cells. WNT family genes begin to transcribe themselves when β-catenin builds up in the nucleus[27]. The JAK/STAT pathway triggers proliferation through the JAK phosphorylation modulate STAT protein resulting in STAT translocation from the cytoplasm to the nucleus causing transcription gene modulation that plays a role in proliferation[28].

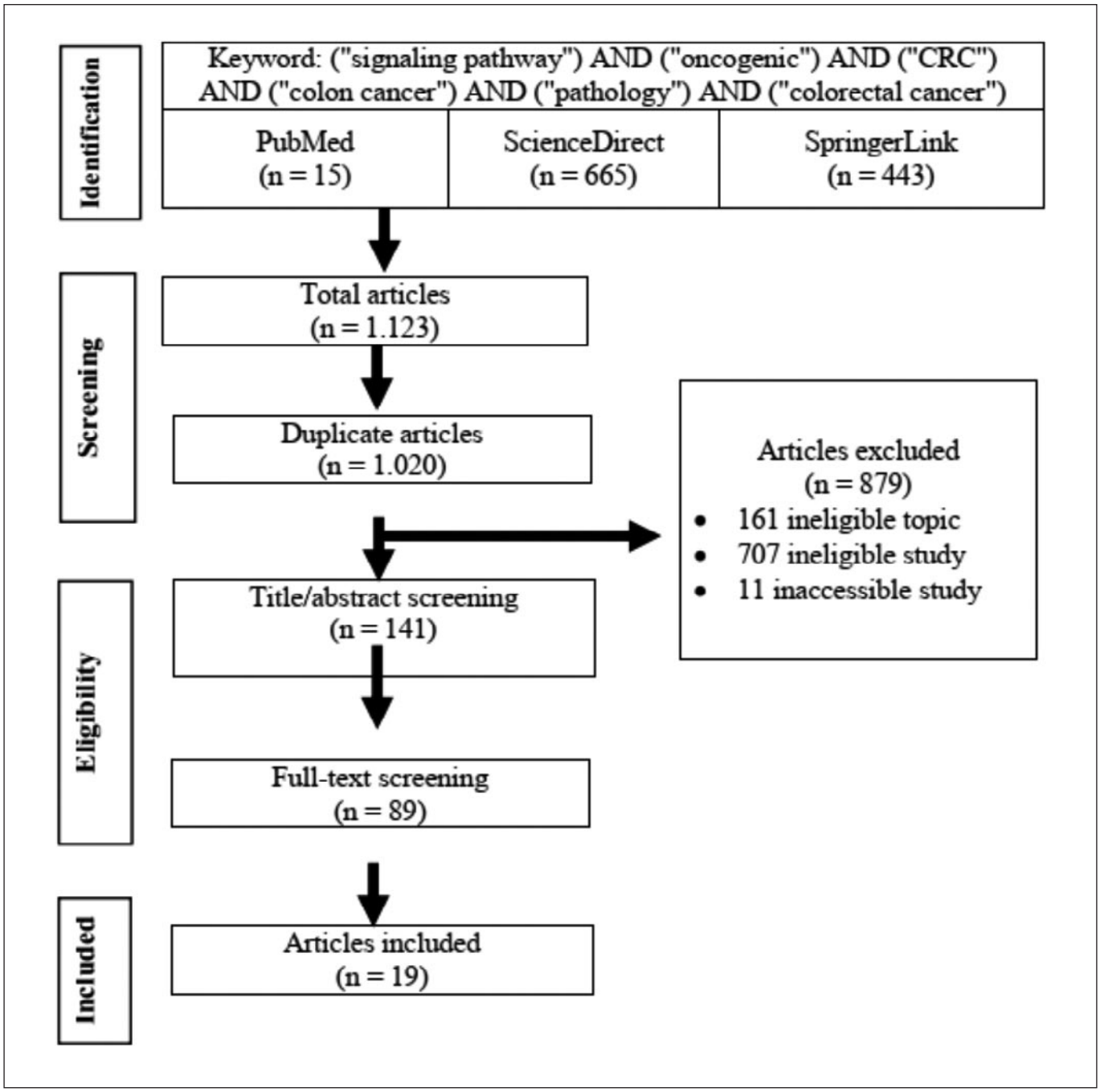

Fig. 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart

The ErBb pathway is also known as the EGF receptor family type I and is included in the Receptor Tyrosine Kinase (RTK) group which can stimulate many signaling pathways and trigger proliferation[29]. The NF-kB pathway plays a major role in triggering inflammation and the aggregation of proinflammatory chemokines and cytokines. The role of NF-kB signaling in inducing proliferation through stimulation of pathways and other proteins including miRNAs so that it can be concluded that NF-kB does not directly stimulate proliferation[30].

The PI3K/AKT/mTOR pathway inhibits GSK-3 by p-Akt, which plays a role in inhibiting the production of Myc and CCND1. If GSK-3 inhibits by p-Akt, there are accumulation of Myc and CCND1 resulting in increase cell proliferation. PTEN, a regulator of this pathway, is essential for the conversion of PIP3 to PIP2. A mutation in PTEN is one of the causes of enhanced proliferation through this pathway[31]. The RAS/RAF/MAPK pathway promotes proliferation involving the BRAF oncogene and the tumor suppressor gene

Table 1. Summary of Studies

No	Authors	Oncologic Pathway	Samples	Effect
1	Szmida, et al., 2015	ErbB signaling pathway	Human colon cancer tissue	Cell division, migration, adhesion, differentiation and apoptosis
2	Kim, et al., 2013	STAT signaling pathway	Colon cancer cell line (HT-29)	Proliferation, inflammated mediated tumor, angiogenesis
		NF-kB signaling pathway		Inflammation, proliferation,
3	Wang, et al., 2020	HGF/MET signaling pathway	Colon cancer cell line (SW480, HT29, HCT15, HCT116, SW620, LS174t, SW837, LOVO, DLD1, RKO)	Invasion and metastasis
4	Lin, et al., 2017	β-catenin signaling pathway	Colon cancer cell line (SW480, HCT-8, SW620, HCT116, HT-29)	Angiogenesis tumorigenesis
5	Yu, et al., 2016	Wnt/β-catenin signaling pathway	Colon cancer cell line (CaCO2, DLD-1, HCT116, LOVO, LS180, SW480, SW620, SW1116)	Proliferation, inhibit apoptosis, invasiveness
6	Luan, et al., 2022	JNK signaling pathway	Colon cancer cell line (HCT116, LOVO)	Promote proliferation
7	Shang, et al., 2020	TGF-β signaling pathway	Colon cancer cell line (HCT116, SW480)	Proliferation, inhibit apoptosis, differentiation
8	Pan, et al., 2018	MAPK/ERK pathway	Colon cancer cell line (CaCO2, DLD-1, HCT116, HT-29, LOVO, LS180, SW480, SW620)	Proliferation, cell survival, metastasis
9	Zhang, et al., 2020	PI3K/AKT pathway	Colon cancer cell line (HCT116, HT29, SW480, SW620)	Proliferation, inhibit apoptosis
10	Uppada, et al., 2018	Wnt/β-catenin pathway	Colon cancer cell line (HCT116, SW620, SW480, HT29, DLD-1, CaCo2, Ls174T, IEC-6)	Proliferation (cell cycle progression), inhibit apoptosis, migration and invasion
11	Zhang, et al., 2014	TGF-β signalingpathway	Colon cancer cell line (HCT116,HT29, SW480, SW620, LOVO)	Cell differentiation, proliferation, apoptosis, migration and invation
12	Liu, et al., 2022	AMPK pathway	Colon cancer cell line (HT29, HCT8, SW480, Caco2, HCT116, RKO)	Regulating tumor cell proliferation
13	Wang, et al., 2020	RAF/MEK/ERK pathway	Colon cancer cell line (HCT116, HCT15)	Proliferation, differentiation, inhibit apoptosis
14	Fan, et al., 2015	JAK/STAT signaling pathway	Colon cancer cell line (HCT15, HCT116, DLD1, HT29, SW480)	Proliferation, differentiation, inhibit apoptosis
15	Chong, et al., 2022	PI3K/AKT pathway	Colon cancer cell line (HCT116,DLD1, HT29, SW480, LoVo, RKO)	Proliferation, inhibit apoptosis, promote invasion
16	Khare, et al., 2019	Wnt/β-catenin pathway	Colon cancer cell line (HCT116, SW480, HT-29, HCT-15)	Tumor cell proliferation
17	Zhang, et al., 2021	MEK/ERK signaling pathway	Colon cancer cell line (RKO,HCT116, SW1116, SW620, HT29,Caco2, LoVo)	Cell growth, differentiation, metastasis
18	Fricke, et al., 2017	TGF-β signaling pathway	Colon cancer cell line (HCT116, RKO, LOVO)	Metastasis, angiogenenisis
19	Sarkhosh-Inanlou, et al., 2020	PI3K/AKT pathway	Colon cancer cell line (HCT116)	Proliferation, metastasis
		RAS/RAF/ERK pathway		Proliferation, metastasis

KRAS. BRAF stimulates an increase in GREB1 expression which triggers an increase in proliferation while mutations in KRAS cause a loss of KRAS's ability to suppress the number of cell proliferation resulting in an increase in cell proliferation[32]. The JNK pathway triggers an increase in proliferation by stimulating an increase in c-Jun levels thereby encouraging cells to transition from the G phase to the S phase of the cell cycle[33]. The TGF-β pathway consists of TGF-β1 and TGF-β2 with different functions. TGF-β1 plays a role in triggering proliferation while TGF-β2 suppresses the number of cell proliferation. In colon cancer, TGF-β2 has many roles due to mutations so it has decreased function in suppressing cell proliferation and causing an increase in the number of cell proliferation[34].

Inhibit Apoptosis

Based on the involvement of the oncologic pathway in inhibiting apoptosis, there are 6 oncologic pathways involved, namely: 1) JAK/STAT; 2) ErBb; 3) PI3K/AKT/mTOR; 4) WNT/β-catenin; 5) TGF-β; and 6) RAS/RAF/MAPK. These oncology pathways were described in the 15 articles included[8,12,14,16-18,20-22].

The JAK/STAT pathway inhibits apoptosis through the JAK phosphorylation modulates STAT protein resulting in STAT translocation from the cytoplasm to the nucleus causing transcription gene modulation that plays a role in inhibiting apoptosis[35]. The ErBb pathway inhibits apoptosis by activating other pathways such as the PI3K and MAPK pathways. The PI3K/AKT/mTOR pathway inhibits the process of apoptosis by inhibiting the activation and expression of caspase, stimulating the degradation of proapoptotic proteins, and increasing the expression of anti-apoptotic proteins[36]. WNT/β-catenin pathway inhibits apoptosis through activation and increased expression of transcription factors that play a role in inhibiting apoptosis such as FOXO3[37]. The TGF-β pathway inhibits apoptosis because dysfunction of this pathway causes inhibition of caspase expression and proapoptotic proteins[38]. In contrast, the RAS/RAF/MAPK pathway inhibits apoptosis by increasing the expression of Hypoxia-Induced Factor-1 (HIF-1) and apoptosis executor protein[39].

Invasion and Metastasis

Based on the involvement of the oncologic pathway in triggering invasion and metastasis, there are 7 oncologic pathways involved, namely: 1) JAK/STAT; 2) ErBb; 3) PI3K/AKT/mTOR; 4) HGF/MET; 5) WNT/β-catenin; 6) RAS/RAF/MAPK; and 7) TGF-β. The oncology pathway was described in the 16 articles included[8,10,12,15,17,18,22,24-26].

The JAK/STAT pathway promotes invasion and metastasis by decreasing the expression of proteins that play a role in regulating cell adhesion. When there is a decrease in the number of cell adhesion factors, the bonds between cells weaken so that it is easy for metastasis[28]. The ErBb pathway promotes metastasis by increasing the expression of MMP-2 and MMP-9 as well as vimentin but decreasing the expression of E-cadherin[36]. The PI3K/AKT/mTOR pathway stimulates metastasis by increasing epithelial-mesenchymal transition (EMT) expression, namely vimentin, decreasing E-cadherin expression. EMT transforms the epithelial structure into motile mesenchymal thereby facilitating metastasis[40].

The WNT/β-catenin and TGF-β pathways have the same mechanism as other pathways in inducing metastasis. Metastasis is triggered through increased vimentin EMT expression and decreased E-cadherin[34]. Whereas the RAS/RAF/MAPK pathway promotes metastasis by increasing MMP expression[39].

Angiogenesis

Based on the involvement of oncologic pathways in triggering angiogenesis, there are 4 oncologic pathways involved, namely: 1) JAK/STAT; 2) PI3K/AKT/mTOR; 3) WNT/β-catenin; and 4) TGF-β. These oncologic pathways were described in the 7 articles included[9,11,25]. JAK/STAT, PI3K/AKT/mTOR, WNT/β-catenin, and TGF-β pathway induce angiogenesis in colon cancer by a hypoxic mechanism. All of these pathways induce angiogenesis through increased HIF-1 and VEGF. Hypoxia condition stimulates those pathways to increase VEGF to promote angiogenesis[28].

Diet and Oncologic Pathway

One of the risk factors for colon cancer is adopting a Westernized diet pattern which tends to consume high red meat, high fat, and low fiber. A diet high in red meat is one of the risks of colon cancer because it increases the proliferation of colonic epithelial cells. One of the causes is the high heme iron content in red meat. Heme iron is a nitrosylation agent that plays a role in forming N-nitroso compounds (NOc). NOc is involved through increasing ROS, which triggers DNA damage. The continuous process of DNA damage also occurs due to dysfunction of the p53 gene, which plays a role in DNA repair. It is well known that p53 is related to the oncological pathway in colon cancer[41].

A high-fat diet affects the incidence of colon cancer through the PI3K/AKT and WNT/β-catenin pathways. A high-fat diet is often associated with obesity, an excess BMI characterizes. The high-fat content in the body inhibits the expression of GSK-3, which plays a role in inhibiting Myc and CCND1. If the amount of GSK-3 expression decreases, there will be an increase in Myc and CCND1 which triggers an increase in cell proliferation. This mechanism involves two main oncological pathways from colon cancer, namely PI3K/AKT and WNT/β-catenin[42].

A low-fiber diet in a Westernized lifestyle increases the risk of colon cancer. The fiber in food will be fermented by bacteria in the colon into SCFA. The majority of SCFA produced is

butyrate. SCFA plays a role in reducing the risk of colon cancer by inhibiting proliferation and inducing apoptosis. SCFA affects all oncological pathways that play a role in colon cancer by stimulating cyclin-dependent kinase inhibitory proteins so that the cell cycle stops and reduces cell proliferation. The involvement of SCFA in the induction of apoptosis is linked to increased expression of caspase. In addition, SCFAs influence oncological pathways that play a role in triggering metastasis and angiogenesis by inhibiting MMPs. So, high intake fiber can reduce colon cancer incidence[43].

Strength and limitations

This review gives information about various oncologic pathways that play a role in the tumorigenesis of colon cancer and their mechanisms. Information about the oncologic pathways involved can be taken into consideration by other researchers who wish to develop colon cancer therapies targeting oncologic pathways. In addition, a diet that needs to be avoided in the incidence of colon cancer is high in red meat, high in fat, and low in fiber. The limitations of this study include identifying the oncologic pathway based on the main hallmarks of cancer and the discussion about nutritional diet is limited to diets that are at high risk of colon cancer.

CONCLUSION

Colon cancer can be caused by oncologic pathways with several different mechanisms, according to the hallmarks of cancer. Based on the quantity of this review, the majority of the oncologic pathways involved are the WNT/β-catenin and PI3K/AKT pathways with the most common mechanisms in tumorigenesis in the form of increased proliferation and inhibition of apoptosis. Several other oncologic pathways, namely: RAS/RAF/MAPK, JAK/STAT, TGF-β, ErbB, NF-kB, HGF/MET, and JNK pathway. Nutrition in the form of a high diet in red meat, high in fat, and low in fiber also affects the hyperactivation of oncologic pathways, thereby increasing the risk of colon cancer.

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