REVIEW

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Risk Factors for Recurrent Colorectal Polyps

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The recurrence of colorectal polyps is caused by various factors and leads to the carcinogenesis of colorectal cancer, which ranks third in incidence and fourth in mortality among cancers worldwide. The potential risk factors for colorectal polyp recurrence have been demonstrated in multiple trials. However, an article that pools and summarizes the various results is needed. This review enumerates and analyzes some risk factors in terms of patient characteristics, procedural operations, polyp characteristics, and dietary aspects to propose some effective prophylactic measures. This review aimed to provide a reference for clinical application and guide patients to prevent colorectal polyp recurrence in a more effective manner. **(Gut Liver 2020;14:399-411)**

Key Words: Recurrence; Colorectal neoplasms; Adenomatous polyps

INTRODUCTION

Colorectal polyps are protrusion lesions that project from the mucosal surface to the colorectal lumen.[1] Different types of polyps can manifest, with occurrence rates ranging from 1% to 43%.[2] Colorectal cancer (CRC), more than one million cases of which are diagnosed annually (with a fatality rate of about 50%), is a common consequence of adenoma recurrence and is an economic burden for society.[3] Based on the World Health Organization (WHO) classification, polyps can be divided into four types: adenomatous, inflammatory, hyperplastic, and hamartomic polyps.[4] Due to the high risk of adenoma-carcinoma sequence, resection is suggested for colorectal polyps.[5,6] However, polyps often recur, at a rate of 20% to 50%.[2] There is a consensus concerning the carcinogenic factors of colorectal polyps, but it is still unclear whether the factors that cause carcinogenesis are similar to those that cause recurrence of polyps. Therefore, it is necessary to elucidate the causative factors of polyp recurrence.

Various factors could contribute to polyp recurrence. Sex, lifestyle (e.g., smoking or drinking habits, and dietary habits), and age of the patient, and the growth site, number, size, and pathological pattern of the polyp are potential risk factors for polyp recurrence. Genetic and environmental factors will be summarized in a cooperative or separative manner here. This review aims to summarize risk factors and underlying mechanisms associated with polyp recurrence and provide a prospective review of prophylaxis and therapy for patients.

RISK FACTORS FOR RECURRENT COLORECTAL POLYPS

1. Patient characteristics

1) Sex and age

It has been demonstrated worldwide that recurrence of colorectal polyps is related to the sex of the patients. The recurrence rate of colorectal adenomatous polyps for male patients is higher than that for female patients (odds ratio [OR], 1.20; 95% confidence interval [CI], 0.83 to 1.61; p=0.04).[7] The mechanism of recurrence could be related to the higher concentration of estrogen/progestogen in female patients than in male patients. Estrogen/progestogen has antagonistic effects on cell hormonal receptors, decreasing the recurrence rate for colorectal polyps among female patients.[7,8]

Age is an essential factor for colorectal polyp recurrence. Patients aged more than 60 years also have higher recurrence rates of colorectal adenoma.[9] The recurrence rate is increasingly related to age, especially, in the proximal colon.[10] In most cases,

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the recurrence of colorectal polyp is associated with continuously mechanical and inflammatory stimulation. Given the high incidence of colorectal dysfunction and constipation, elder patients are more at risk of undergoing stimulations of colorectal tract, leading to chronic inflammation.[11,12] Traditional Chinese medicine explained the recurrent colorectal polyps by "deficiency of YANG, excess of YIN."[13] "Deficiency of YANG" refers to the differentiative ability of colorectal mucous cells is decreased with the aging of patients. "Excess of YIN" means that the excessive proliferation of colorectal mucous cells. Accompanied by the dysfunction of the immune system, this hypothesis might be a more indirect proof that age can contribute to the recurrence of colorectal polyps. Clinically, different countries have distinctive criteria to definite susceptible patients as "elder individuals." Compared with 60 years of age in the West, 50 years is the most accurate boundary for Asian patients, who manifest a higher recurrence rate of colorectal polyps with high prevalence of hypertension (OR, 2.44; 95% CI, 1.34 to 4.45; p=0.004).[9]

2) Past history

Recently, it was proposed that recurrent colorectal polyps might be associated with patients' disease history.[14,15] Some studies have shown that colorectal adenoma recurrence may transform as a consequence of inherited genetic predisposition for familial adenomatous polyposis of CRC (OR, 2.25; 95% CI, 1.32 to 3.84; p=0.02).[16] Barrett's esophagus and ulcerative colitis, regarded as premalignant disorders of colorectal adenoma, are potential risk factors for adenocarcinoma and progression to high-grade dysplasia,[17,18] similar to polyp recurrence.[19]

3) Obesity and body mass index

Multivariate analysis has demonstrated that obese patients might have higher recurrence rates than nonobese patients (OR, 7.61; 95% CI, 1.58 to 36.48; p=0.011).[20] Possibly, the biological mechanism is that obesity elevates the expression level of insulin and insulin-like growth factor-1, thus stimulating the transformation of non-advanced colorectal polyp into advanced stage and triggering recurrence.[20] Clinically, patients who exercise at least 1 hour per week are more likely to have a low recurrence rate of colorectal polyps (OR, 0.34; 95% CI, 0.14 to 0.81; p=0.015).[21] Notably, only for the male patients, sedentary behavior represents a potential risk for colorectal adenoma recurrence (OR, 1.47; 95% CI, 1.03 to 2.11; p=0.03).[22] Considering the cardiac function, patients with high resting heart rate (≥81 beats/min) manifest high risk of advanced adenoma recurrence (OR, 6.18; 95% CI, 1.18 to 32.37, p=0.03).[23]

Body mass index (BMI) and the proportion of visceral fat tissue in the abdominal wall are common parameters of obesity and are relatively valid parameters.[24] A large BMI is associated with an increasingly potential risk of advanced colorectal polyp recurrence (OR, 1.62; 95% CI, 1.04 to 2.53; p=0.04).[16] However, BMI may not be a precise parameter for describing the degree of obesity.[25] For example, with aging, patients' muscle tissue undergo atrophy and can show a false-negative predisposition, especially with BMI ≥30 kg/m^2 (OR, 1.17; 95% CI, 0.92 to 1.48; p=0.04).[16] Therefore, the American Society of Bariatric Physicians suggested that BMI and visceral fat deposition should be used as one criterion for recurrence determination. Visceral fat deposition can induce some dysregulation of the body processes, including insulin resistance and hyperinsulinemia.[24] The possible mechanism is that the greater the proportion of visceral adipose tissue, the more inflammatory factors can be released, including interleukin-6 (IL-6), tumor necrosis factor-α, C-reactive protein, and serum adipocytokines (include leptin and adiponectin), which might lead to the recurrence of colorectal adenoma.[12,26]

4) Cigarette and alcohol preference

Cigarettes have a substantial number of components, such as polycyclic aromatic hydrocarbons, heterocyclic amines and nitrosamines, with carcinogenic action.[27] As an independent potential risk factor of colorectal adenomatous polyp recurrence, cigarette smoking can lead to oxidative stress and DNA damage, producing various carcinogens.[27] Carcinogens that present along the colorectal mucosa by passive ingestion or the circulatory system, can combine with DNA to form DNA adducts, interrupt the cellular replication, and inhibit the DNA repair process.[28] The CO in tobacco smoke can trigger the production of the carbonyl hemoglobin, leading to hypoxia, DNA damage, and lipid or protein deterioration.[29] Several factors contribute to the degree of the damage caused by smoking, such as the duration and amount of the smoking, which is related to the occurrence of colorectal polyps.[30] The recurrence rate of adenomatous polyps is significantly increased in patients with a history of smoking for longer than 35 years (OR, 2.88; 95% CI, 2.06 to 4.01; p=0.001).[31]

Excessive alcohol consumption might directly contribute to the recurrence of colorectal adenomatous and colonic hyperplastic polyps (OR, 1.67; 95% CI, 1.05 to 2.21; p=0.003).[32] Clinically, alcohol intake volume, when it is larger than 51.3 g/day, has a positive relationship with the occurrence of rectal adenomatous polyps.[31,32]

5) Nonsteroidal anti-inflammatory drugs

Although the pharmacological mechanisms of nonsteroidal anti-inflammatory drug (NSAID) intake and colorectal adenoma recurrence are not completely understood, it is possible that NSAIDs can decrease colorectal polyp recurrence.[33] However, many studies did not demonstrate the same results, which might be because the small sample size has limited the analysis process.[34]

An increasing number of new drugs are produced on the basis of the mechanism that NSAIDs can inhibit cyclooxygenase (COX), producing an anti-inflammatory action and decreasing

the recurrence rate of the polyps (OR, 0.77; 95% CI, 0.63 to 0.95; p=0.02).[35,36] The most commonplace nonselective COX inhibitor is aspirin, which can inhibit carcinogenesis, showing a long-term pattern in reducing the recurrence risk.[37] Maintaining a low-dose and long-term intake of aspirin can obviously reduce the recurrence of colorectal adenoma after 1 year but not longer than the fourth year, given that chemoprevention by aspirin can only be achieved after long-term drug consumption.[37,38] Celecoxib, a selective NSAID, may inhibit colorectal adenoma recurrence (OR, 0.38; 95% CI, 0.16 to 0.89; p=0.03).[35,39] Notably, various genotypes can contribute to differences in cardiovascular toxicity for celecoxib in patients, such as PGES, CRP, SRC, and GPX3 combined with a high risk for being poisoned.[40]

6) Gene polymorphism

Gene variation may confer a potential risk for colorectal adenoma recurrence, manifesting as gene polymorphism. Most of the gene polymorphisms can only produce an effect when combined with dietary bioactive materials; this is referred to as gene-diet interaction.

IL single-nucleotide polymorphisms (SNPs) may be associated with the risk of colorectal adenoma recurrence.[41] The individual who has specific IL genotype, with a low serum IL concentration, may manifest a high colorectal adenoma recurrence rate. For example, the concentration of IL-6 was inversely related to the high-risk and advanced adenomatous polyp recurrence rate.[42] The *IL1B-31* (*C>T*) heterozygotic carriers manifested higher recurrent rate of colorectal adenoma compared with homozygous allele (OR, 1.8; 95% CI, 1.2 to 2.9; p=0.02).[43] Patients homozygous for *IL-10-592 C* (OR, 2.23; 95% CI, 1.07 to 4.66; p=0.03) or *IL-10-891* C genotype (OR, 2.18; 95% CI, 1.05 to 4.51; p=0.05) manifest high recurrence risk, with a high concentration of serum IL-10.[41] In addition, taking gene-diet interaction into consideration, the regular NSAID users who have an *IL-10-1082 G>A* variant may have higher colorectal adenoma recurrence rate (OR, 1.55; 95% CI, 1.00 to 2.43; p=0.01).[44] The mechanism is that the IL-10, which is an essential cytokine with immunosuppressive and anti-inflammatory properties, can inhibit other cytokines, such as IL-6, IL-8 and IL-12.[45] With the reversal of the original inhibition of apoptosis and cell proliferation, the *IL-10-1082 G>A* variant can initiate the recurrence process of adenomas.[46]

The D2 dopamine receptor (DRD2) gene polymorphism might be associated with a lower recurrence rate of colorectal adenoma.[47] Two kinds of variants, the *rs1799732 CT* (OR, 1.30; 95% CI, 1.01 to 1.69; p=0.03) and *rs1800497 TT* (OR, 2.40; 95% CI, 1.11 to 5.20; p=0.02), are significantly associated with the recurrence of advanced adenomas.[47] Alcohol addiction may play a role in differing results between DRD2 *rs1799732* and *rs6277* genotypes. There are two possible mechanisms to interpret this interaction. The DRD2 polymorphism can decrease the number of dopamine receptors in the colonic mucosa, contributing to the reduction of the cyclic AMP inside the cells, thereby inhibiting proliferation.[48] The high expression of dopamine receptors, located in the pancreatic β cells, can inhibit glucose-induced insulin secretion, thereby modulating the potential risk for recurrence.[49]

Race is the most obvious performance indicator of gene polymorphism. When it comes to race-ethnicity, racial gene variant is not a potential risk factor of colorectal adenoma recurrence between blacks and whites (39.2% vs 39.4%: OR, 0.98; 95% CI, 0.80 to 1.20; p=0.02).[50]

Cytochrome enzyme is an essential cellular bioactive component that can catalyze various biochemical processes. In particular, *CYP24A1* is a polymorphic version of the cytochrome enzyme genes, manifesting positive association with the 25-hydroxycholecalciferol [25(OH)D] (p=0.02).[51] More copies of the T allele in *CYP24A1 rs927650* contribute to high recurrence of any colorectal adenomas, for heterozygotes (OR, 1.30; 95% CI, 0.99 to 1.70; p=0.04) and homozygotes (OR, 1.38; 95% CI, 1.01 to 1.89; p=0.04), respectively.[51] When the gene polymorphisms cooperate with vitamin D metabolites, the effect can be enhanced. Other polymorphism, namely *CYP24A1 rs35051736*, has been reported that has positively statistical significance with advanced colorectal adenoma (p<0.001).[51] In addition, CYP2C9 genotype has positive association with recurrent adenoma of 29% (OR, 1.29; 95% CI, 1.09 to 1.51; p=0.04) for *rs1799853* and 47% (OR, 1.47; 95% CI, 1.19 to 1.83; p=0.04) for *rs1057910* allele.[52]

Cyclooxygenase-2 (COX-2) is the committed enzyme for production of prostaglandins, mediating inflammatory events. Two SNPs of COX-2 can contribute to high recurrence rate of colorectal adenoma. The *rs5277* which exhibits homozygous genotype of the minor C allele can increase 51% recurrent risk (OR, 1.51; 95% CI, 1.01 to 2.25; p=0.02), and the *rs4648310* as a heterozygote of the minor G allele can increase 37% risk of recurrent adenoma compared with AA genotype (OR, 1.37; 95% CI, 1.05 to 1.79; p=0.03).[53]

2. Characteristics of polyps

1) Growth site of the polyp

The recurrence of intestinal polyps is related to their growth site.[54] Colorectal polyps, which are located in proximal (right-sided) and ascending colon, show a greater tendency for recurrence than distal (left-sided) polyps (OR, 1.6; 95% CI, 1.2 to 2.3; p=0.02).[4] Many researchers in Asia could not achieve the same statistical results as European investigators.[1,6] The reasons for this difference are as follows. Firstly, limited analysis results owing to less sample capacity caused by multiple reasons, such as shorter retrospective analysis duration, limited source of the case report, less adherence to the doctors' instructions by the patients, and absence of regular follow-up of the patient's condition. Secondly, differences of racial, daily diet and living habits between Asian and Western countries. For familial adenoma-

tous polyposis, patients who have resection in the ileal pouch or cuff after ileal pouch-anal anastomosis may have higher recurrence of colonic polyps.[55]

2) Number and size of polyps

The hypothesis that recurrence would increase among patients with more than three colorectal polyps is widely accepted (OR, 2.25; 95% CI, 1.20 to 4.21; p<0.001).[56] Statistical studies demonstrated that the increasing number of colorectal polyps can facilitate their rapid growth.[57] Colorectal adenoma resection is possibly associated with the risk of adenoma recurrence only after 3 years, located on the previous screening site.[58]

The size of colorectal polyps may be a potential risk factor for adenoma recurrence. The faster growth and greater proportion of the villous structure of adenoma with a diameter of ≥1 cm appear to be linked to high recurrence.[59] The villous structure of adenomas has a large superficial area and high hyperplastic level, which may be a possible reason for the higher recurrence.[60] Generally, recurrence is most common in polyps with a diameter of ≥10 mm,[54] and least common among patients with polyps with a diameter of ≤5 mm (OR, 2.07; 95% CI, 1.56 to 7.60; p=0.002).[61] More recently, lesion occupying ≥75% of the luminal circumference has been conducted as an independent risk factor of recurrent adenoma (OR, 5.6; 95% CI, 2.4 to 12.9; p<0.001).[62]

Whether the size can be an indicator of the colorectal polyp recurrence or not remains controversial.[54]

3) Histological pattern of polyps

There is a consensus in the field that dysplasia predicts the risk of the progression to carcinogenesis via serrated or microsatellite mutation pathway.[5,63] High-grade dysplasia is related to colorectal adenoma recurrence.[64] Patients who have multiple adenomas combined with synchronous hyperplastic polyps manifest a higher recurrence rate than patients who just have adenoma at baseline (75% vs 21%).[65] It may be that the number of the sample is too small to observe the precise association.[66] With high criticality, advanced adenomatous polyps have a higher recurrence rate than do non-advanced polyps (34.4% to 41.1% vs 4.4% to 6.5%), and the highest rate with diameter ≥15 mm (approximately 57.9% recurrence rate).[66]

For adenomatous polyps, both villous and tubulovillous adenomas have high recurrence rates, with the former having the highest recurrence rate (OR, 1.55; 95% CI, 1.06 to 2.25; p=0.003).[67] The distinguishable criterion among the tubular, tubulovillous, and villous adenoma is the proportion of villous structure. Although tubular adenoma outnumbers other types of adenomas in terms of colonoscopy surveillance, its recurrence rate ranks the lowest (p=0.03).[68] Villous adenomas have a high proportion of dysplastic hyperplasia among the epithelium and glands, which proves further indirect evidence that the more villous tissue patients have higher their risk of colorectal polyp recurrence. For pathological patterns, the sessile serrated adenoma might contribute to the recurrence of multiple adenomas.[69] Therefore, the aforementioned parameters should be considered together as a complication, combining size and pathological patterns with those of dysplastic hyperplasia.[70]

3. Procedural factors

1) Post-polypectomy follow-up

The follow-up schedule is performed as a surveillance method to investigate the recurrence rate among patients. Many statistical articles have proved that post-polypectomy follow-up can decrease the recurrence risk of colorectal polyps.[71,72] Particularly, the adenomatous polyp is the most common neoplastic outcome of follow-up screening and artificial removal (resection) may lead to recurrence.

By assessing the severity of the polyps, many guidelines stratify the adenomatous polyp into two groups: low-risk adenomas (LRAs)/non-advanced stage and high-risk adenomas (HRAs)/advanced stage.[57] The LRAs have one or two adenomatous polyps with a diameter of <10 mm; HRAs have three or more adenomatous polyps with a diameter of ≥10 mm. The HRAs have severe dysplastic hyperplasia of the villous-state adenomas. The recurrence rate of advanced adenomatous polyps after the first polypectomy is 3.6% in the low-risk group and 38.9% in the high-risk group,[73] which can be explained by the higher incidence of a complicated symptoms (e.g., hematochezia, diarrhea and mucous bloody stool) among high-risk patients.[74] HRAs benefit the most from intensive follow-up.[69] The America's Multi-Society Task Force (MSTF), British Society of Gastroenterology, and Chinese Medical Association issued guides for post-polypectomy follow-up in 2006, 2012, and 2014.[14] These three organizations highlight the same crucial parameter of follow-up: time interval. It depends on the individual's condition to formulate and depicts a positive relationship with the high recurrence rate of the colorectal polyp, respectively manifesting 18%, 23%, 31%, 40% in the end time of 2, 3, 5, and 10 years.[75] Different countries have inconsistent protocols to obey. For instance, in the MSTF system, the time interval for HRAs to follow-up is ≤3 years, while for LRAs it is 5 years and even 10 years for patients in whom adenomatous polyps were not detected at the first colonoscopy.[14] What needed to be stressed is that too short a duration between two follow-up checks is not reliable for a correct diagnosis. In addition, high frequency follow-ups for one patient can be wasteful.

2) Quality of polypectomy

Currently, endoscopic polypectomy is the most optimal protocol to resect polyps.[14] Compared with conservative surgery, endoscopy has several advantages (e.g., small wound, few complications, fast rehabilitation, and low cost); the survival rate is up to 90% with appropriate treatment.[76] The quality of the polypectomy is affected by two principal determinants: the ac-

curacy or resolution of the endoscopy and the operator's skill.

Polypectomy can be operated by two main methods: endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). The local recurrence rate for conventional polyps with EMR is approximately 0.8% to 7.2%,[63] and approximately 11.6% to 27% in the colorectal region (OR, 3.2; 95% CI, 1.2 to 8.5; p=0.03).[77,78] In some circumstances, endoscopic piecemeal mucosal resection, a potential independent risk factor, shows a higher recurrence rate up to 20%, compared with the 2% of the *en bloc* resection (OR, 2.43; 95% CI, 1.34 to 5.64; p=0.04).[79] Likewise, the local recurrence rate for the ESD is approximately 4.9% to 7% while the accumulated recurrence rate for both of the techniques can reach to 30% to 45%.[56,80] The recurrence rate of adenomatous polyps peaked in the eighth year after the first polypectomy.[4] Clinically, the wide-field endoscopic mucosal resection (WF-EMR) and full-spectrum endoscopy could be the prospective methods in future polypectomy processes.[81] Although the methods being utilized are various, the recurrence rate of colorectal adenoma is still 35.5% to 50%.[54,56]

In terms of operators, *en bloc* resection is often used to remove small lesions, while the larger ones (diameter ≥2 cm) are often treated in a piecemeal fashion and with ablative techniques. The American Society for Gastrointestinal Endoscopy suggested that the withdrawal time should not be shorter than 6 minutes.[14]

Besides, the prospective management of polypectomy can be restricted to inadequate skills of the operators. For example, the recurrence rate is distinctive between Asian and European patients because of the difference in the *en bloc* resection rate of ESD (88.0% to 98.3% in Asia and 67.1% to 78.6% in central Europe).[80,82] Both the polypectomy techniques that operators perform and perceptions that operators hold can also influence the recurrence of colorectal adenomas.[81]

3) Missed diagnosis of the polyp

As an iatrogenic factor, missed diagnosis has a substantial impact on the recovery process and significant association with recurrence adenoma (OR, 3.4; 95% 1.6 to 7.4; p=0.003).[60] Approximately 15% to 24% of all types of colorectal polyps occur because of missed diagnosis after the first colonoscopy, and 0% to 6% of the polyps have a diameter of ≥10 mm.[83] Missed diagnosis rates of colorectal adenomas, with one, two, and three or more sites of the polyps, is 14%, 28%, 44%, and 66%, respectively.[61]

Locally, the proximal colon has a higher incidence of missed diagnosis than does the distal colon. This difference is related to multiple factors, such as fuzzy view caused by an inadequately prepared colorectal tract, similar characteristics between the neoplasm and polyp, and dexterity and observation ability of the operator.[83] To conclude, missed diagnosis can trigger a false increase in the recurrence, leading to malignant transformation of the previous colorectal polyp. Similarly, it proves the necessity of follow-up for patients who do not have polyp recurrence after the first colonoscopy.

4. Daily diet

1) Dietary fiber

Increasing the proportion of dietary fiber, particularly fiber cereal and whole grains, in an individual's daily diet can reduce the recurrence rate of colorectal adenomas.[84] Similar to the carcinogenesis process, the possible mechanism is that the fiber undergoes glycolysis mediated by anaerobic bacteria and thus can be oxidized and transformed into short chain fatty acid. This fatty acid plays a key role in restraining cell proliferation and facilitating apoptosis or cell differentiation.[20] However, soluble dietary fiber (e.g., cellulose in fruits) might prevent the recurrence of the adenomatous polyps (OR, 0.65; 95% CI, 0.47 to 0.92; p=0.02), while the insoluble dietary fiber in various vegetables or wheat may not (OR, 0.88; 95% CI, 0.35 to 1.57; p=0.28).[20]

2) Dry beans

Consumption of legumes, which include dry beans, dry peas, green beans, and peanuts, can reduce the recurrence rate of colorectal adenoma (OR, 0.35; 95% CI, 0.18 to 0.69; p=0.001).[85] Dry beans have a negative association with advanced colorectal adenoma recurrence.[86] Given that dry beans have high amounts of nutrients and bioactive components, which prevent carcinogenesis,[87] the mechanism by which they protect against polyps is that some non-digestible carbohydrates are transformed into butyrate, which could medicate the antineoplastic and anti-inflammatory process, thus arresting the recurrence process of polyps.[88]

3) Folic acid

Folate, a necessary component for DNA synthesis and repair, has a corresponding relationship with CRC risk.[89] And low serum folate can increase recurrence rate of colorectal adenoma (OR, 1.34; 95% CI, 0.32 to 1.74; p=0.002).[90] In particular, ingesting less folate might mediate the carcinogenesis by abnormal gene expression and genetic instability. Recently, a contrary view has been proposed: a low-folate diet habit cannot induce the recurrence of colorectal adenoma independently.[91] Methylenetetrahydrofolate reductase (MTHFR) is an essential regulatory enzyme participating in the folate synthesis pathway. A C/T transition, located in 677 encoding gene position, of the MTHFR (*MTHFR C677T*) could increase colorectal adenomatous polyps' recurrence when accompanied with folate consumption (OR, 1.30; 95% CI, 1.00 to 1.81; p=0.04).[92] Thus, this inference is only possible in patients who undergo 4 years post-randomization or have folate consumption below the local median level.[93]

4) β-Carotene

β-Carotene supplementation might impact on the recurrence of colorectal adenoma, either in an increasing or decreasing

manner.[94] Among patients who have neither smoking nor alcohol preference, β-carotene consumption decreases the recurrent rate of adenomas (OR, 0.56; 95% CI, 0.35 to 0.89; p<0.001). Interestingly, for the patients who smoked cigarettes with more than one drinking per day, β-carotene doubly contributes to adenoma recurrence (OR, 2.07; 95% CI, 1.39 to 3.08; p<0.001).[94]

β-Carotene might achieve anti- or pro-oxidant properties in different circumstances,[95] modulating DNA methylation, and arresting the DNA replication process, but the mechanism is not completely understood. Simultaneously, β-carotene can play a supplementary role in the recurrence of colorectal adenoma, such as in patients who have been smoking or drinking for a long time.

5) Red meat

Red meat consumption is positively associated with multiple colorectal adenomas recurrence, albeit the relevance is possibly inaccurate.[96,97] Significantly high recurrence of advanced polyps was contributed by overeating either pan-fried red meat (OR, 1.85; 95% CI, 1.10 to 3.13; p=0.02) or well-done red meat (OR, 1.71; 95% CI, 1.02 to 2.86; p=0.03).[96] For recurrence of multiple adenomas, significant positive associations were observed as follows: pan-fried red meat (OR, 1.63; 95% CI, 1.01 to 2.61; p=0.03), well done red meat (OR, 1.68; 95% CI, 1.03 to 2.74; p=0.04).[96]

A possible biologic mechanism is that cooked (either pan-fried or well-done) red meat produces genotoxic material termed heterocyclic amines. This mutagen can trigger the covalent modification of the DNA/DNA adduct generation process in guanine site, leading to the mutation.[96]

6) Flavonols

Flavonols, which exist in some vegetables, fruits, and tea, are a type of bioactive polyphenol materials.[98] Consuming dietary flavonols (>30 mg/day) may decrease the recurrence rate of colorectal adenomas.[98] A diet that is high in flavonols, combined with IL SNPs, might have an even greater decreased effect on the recurrence rate of adenomatous polyps.[41] For example, patients whose genotype is *IL-6-174 GG* may have a lower recurrence rate of colorectal adenomas, combined with great flavonols consumption (OR, 0.14; 95% CI, 0.03 to 0.66; p=0.02). On the contrary, individuals with *IL-6-174* SNP, thus preventing adenoma recurrence by altering the transcription of IL-6, may have high recurrence with excessive intake of flavonols.[41,98] The possible mechanism is that the SNPs in the promotor site of the genes encoding IL-1β, IL-6, IL-8, and IL-10 are effective at reducing the expression of these ILs, leading to the proliferation and carcinogenesis of mucosa cells.[42,99]

7) Vitamin D, calcium, and milk

High calcium consumption might decrease the carcinogenic risk of colorectal polyps.[100] A randomized trial showed that the calcium intake of high-risk patients can manifest a modest, but preventive, effect against colorectal adenoma recurrence (OR, 0.64; 95% CI, 0.47 to 0.88; p=0.005). Consumption of calcium as supplementation (3 g/day for approximately 4 years) can decrease recurrence by 24%,[100] mediated by calcium binding to the bile/lipids, thereby inhibiting the colonic epithelial cells proliferation.[101]

Subsequently, when both drugs and dietary factors are considered together, it is possible that the colorectal recurrence can be managed. For example, vitamin D and calcium might work in a cooperative manner to reduce the recurrence rate of colorectal adenoma.[102] Calcium combined with aspirin may also have the same impact.[103] The preventive effect of high calcium consumption can only be observed among patients with high circulating concentrations of vitamin D.[104] With intake of a dairy product, the vitamin D plus calcium can inverse the high recurrence rate for adenoma. In terms of gene-diet interaction, further studies ought to be done to investigate the interaction between ApaI genotype and dairy diet (milk) consumption.[105]

8) Lignin

Lignin, which is a plant polyphenol material, is related to the preventive effects on colorectal carcinogenesis.[106] A sex-specific analyses indicated that high lignin consumption of lignin can increase the risk of any adenoma recurrence only in female patients (OR, 2.07; 95% CI, 1.22 to 3.52; p=0.004).[107] The possible mechanism is that the dietary lipid can impact the metabolism process of lignin, arresting transformation to more bioactive material (enterolactone and enterodiol) and blocking steroid hormone secretion.[108]

9) "Vigor Retention and Spleen Debility"

From a traditional Chinese medicine viewpoint, an unbalanced diet is the main reason for the colorectal polyp recurrence. Restricted food consumption may trigger constipation and stimulate the intestinal tract, that is "Vigor Retention." Unhygienic dietary habits may impact the functioning of the spleen, leading to the suppressive function of peripheral immune system, thereby causing the recurrence ("Spleen Debility"). Finally, a mixed substance can form, which consists of phlegm and blood stasis, and trigger the recurrence of colorectal polyps.

10) Homocysteine

The progressive serum homocysteine concentration can be an independent factor for high-risk colorectal adenoma recurrence (OR, 2.26; 95% CI, 1.30 to 3.94; p=0.02).[109] Previous reports have indicated that the circulating homocysteine has the capacity to produce highly reactive metabolites that are positively related to some diseases (e.g., hyperinsulinemia, chronic inflammation, and carcinogenesis).[110] With daily diet, patients who choose a low fat that is high in fiber, fruits, and vegetables (high flavonols and folate) are more likely to decrease their

Table 1. The Statistical Risk Factors of Recurrent Colorectal Polyps

Risk factors	Qualified risk	
	OR (95% CI)	p-value
Patient characteristics		
Male sex	1.20 (0.83–1.61)	0.040
Sedentary behavior	1.47 (1.03–2.11)	0.030
Age (>60 yr, with hypertension)	2.44 (1.34–4.45)	0.004
Past history (FAP)	2.25 (1.32–3.84)	0.020
Obesity	7.61 (1.58–36.48)	0.011
Exercise (>1 hr/wk)	0.34 (0.14–0.81)	0.015
Resting heart rate (>81 beats/min)	6.18 (1.18–32.37)	0.030
Body mass index (≥30 kg/m^2)	1.17 (0.92–1.48)	0.040
Cigarette smoking	2.88 (2.06–4.01)	0.001
Alcohol preference	1.67 (1.05–2.21)	0.003
NSAID intake	0.77 (0.63–0.95)	0.020
IL-10-1082 G>A*	1.55 (1.00–2.43)	0.01
Celecoxib	0.38 (0.16–0.89)	0.030
Gene polymorphism		
IL1B-31 (C>T) heterozygotes	1.80 (1.20–2.90)	0.020
IL-10-592 C homozygotes	2.23 (1.07–4.66)	0.03
IL-10-891 C homozygotes	2.18 (1.05–4.51)	0.05
DRD2 rs1799732 CT	1.30 (1.01–1.69)	0.03
DRD2 rs1800497 TT	2.40 (1.11–5.20)	0.02
CYP24A1 rs927650 T heterozygotes	1.30 (0.99–1.70)	0.04
CYP24A1 rs927650 TT	1.38 (1.01–1.89)	0.04
CYP2C9 rs1799853	1.29 (1.09–1.51)	0.04
CYP2C9 rs1057910	1.47 (1.19–1.83)	0.04
COX-2 rs5277 CC	1.51 (1.01–2.25)	0.02
COX-2 rs4648310 G heterozygotes	1.37 (1.05–1.79)	0.03
Race (blacks and whites, 39.2% vs 39.4%)	0.98 (0.80–1.20)	0.02
Polyps characteristics		
Proximal (right-sided) and ascending colon	1.6 (1.2–2.3)	0.02
Number (≥3)	2.25 (1.20–4.21)	<0.001
Diameter (≤5 mm)	2.07 (1.56–7.60)	0.002
Lesion occupying (≥75% of the luminal circumference)	5.6 (2.4–12.9)	<0.001
Villous structure	1.55 (1.06–2.25)	0.003
Procedural factors		
Conventional EMR	3.2 (1.2–8.5)	0.03
EPMR	2.43 (1.34–5.64)	0.04
Missed diagnosis	3.4 (1.6–7.4)	0.003
Daily diet†		
Dietary fiber (insoluble)	0.88 (0.35–1.57)	0.28
Dietary fiber (soluble)	0.65 (0.47–0.92)	0.02
Dry beans	0.35 (0.18–0.69)	0.001
Folate (low serum concentration)	1.34 (0.32–1.74)	0.002
MTHFR C677T*	1.3 (1.00–1.81)	0.04

Table 1. Continued

Risk factors	Qualified risk	
	OR (95% CI)	p-value
β-Carotene		
Non-smoker	0.56 (0.35–0.89)	<0.001
Smoker with alcohol preference	2.07 (1.39–3.08)	<0.001
Red meat (for advanced adenoma)		
Pan-fried red meat	1.85 (1.10–3.13)	0.02
Well-done red meat	1.71 (1.02–2.86)	0.03
Flavonols		
IL-6-174 GG*	0.14 (0.03–0.66)	0.02
Vitamin D, calcium, and milk	0.64 (0.47–0.88)	0.005
Lignin (female)	2.07 (1.22–3.52)	0.004
Serum homocysteine	2.26 (1.30–3.94)	0.02
Serum ferritin (>70 μg/L)	1.39 (0.96–2.02)	0.04
Prophylaxis		
Hormone replacement therapy	0.58 (0.35–0.87)	0.02
Selenium supplementation	0.82 (0.71–0.96)	0.01
Metformin	0.57 (0.39–0.85)	0.006
Low-dose aspirin	0.75 (0.59–0.96)	0.02
Ursodeoxycholic acid	0.61 (0.39–0.96)	0.03

OR, odds ratio; CI, confidence interval; FAP, familial adenomatous polyposis; NSAID, nonsteroidal anti-inflammatory drug; IL, interleukin; EMR, endoscopic mucosal resection; EPMR, endoscopic piecemeal mucosal resection.
*The particular genotype of a patient who consumed a diet or received drugs that differed from the genotype in the left column; †The maximum preventive effect of each dietary factor.

serum concentration of homocysteine, with a lower colorectal adenoma recurrence rate.[89] Whereas, few studies have published inconsistent results of serum homocysteine.[111] Accumulated circulating homocysteine might trigger nuclear factor (NF)-κB activation, leading to stimulation of the proinflammatory cytokines and expression of cancer promoting factors. Similarly, elevated serum homocysteine might shift the proliferation and methylation pathway to a mutation state, altering the one-carbon metabolism and exhibiting carcinogenesis action.[112]

11) Dietary iron

High concentration of serum ferritin (>70 μg/L), which is a derivate of dietary iron, could modestly elevate the recurrence rate of colorectal adenoma (OR, 1.39; 95% CI, 0.96 to 2.02; p=0.04).[113]

PROPHYLAXIS FOR RECURRENCE OF POLYPS

For dietary factors, the low-fat and high-fiber diet with high intake of fruits and vegetables may reduce the colorectal adenoma recurrence rate, even among patients who do not use NSAIDs (OR, 0.87; 95% CI, 0.69 to 1.09; p=0.03).[114] A mineral-rich red algae substance (Pallas), which has been demonstrated to block the mice's nutritional supplement to primary adenomatous polyp and inhibit the recurrence, may be a prospective treatment.[11] Recently, it has been shown that daily consumption of 2 g eicosapentaenoic acid (EPA), an omega-3 polyunsaturated fatty acid, for 6 months can minimize the number and size of rectal adenomas.[115] Combined with aspirin (300 mg/day), this regimen might have some chemopreventive function on colorectal adenoma burden.[116] However, investigators should perform further behavioral tests to assess the safety of various drugs or healing therapies. Selenium supplementation can reduce up to 18% recurrence rate of advanced colorectal adenoma with great preventive effect (OR, 0.82; 95% CI, 0.71 to 0.96; p=0.01).[117]

For colonoscopy, complete excision and repeat examinations might decrease the colorectal adenoma recurrence rate.[2] For the high-risk group patients, with baseline adenoma, 3 yearly surveillance may be prioritized.[80] Conversely, some patients with advanced colorectal adenoma ought to follow a more frequent surveillance schedule.[4] Given that post-polypectomy follow-up can be a tremendous burden on therapy units and patients, the follow-up surveillance should be arrested at 75 years of age.[118]

Hormone replacement therapy might decrease the recurrence rate for female patients who are aged >62 years (OR, 0.58; 95% CI, 0.35 to 0.87; p=0.02).[116] Calcium and aspirin can have a preventive effect on advanced adenomatous polyps recurrence.[102]

Diabetic patients who take metformin can have a lower risk of colorectal adenoma recurrence (OR, 0.57; 95% CI, 0.39 to 0.85; p=0.006).[119] In addition, the preventive drugs such as celecoxib for either 800 mg/day (OR, 0.61; 95% CI, 0.45 to 0.83; p=0.03) or 400 mg/day (OR, 0.70; 95% CI, 0.55 to 0.87; p=0.03) and low-dose aspirin (OR, 0.75; 95% CI, 0.59 to 0.96; p=0.02) were significantly associated with a decreased recurrence rate of colorectal adenoma.[120] The ursodeoxycholic acid (UDCA) is a promisingly chemopreventive drug for recurrence of colorectal adenoma. Compared patients who received placebo, the UDCA treated patients manifested a low recurrence rate of adenoma (OR, 0.61; 95% CI, 0.39 to 0.96; p=0.03) (Table 1).[121]

In general, the prophylaxis for polyp recurrence is a comprehensive regimen and the optimal scheme requires the most precise medical therapy. More studies are needed to validate the effective management of recurrence and address multiple questions.

FUTURE RESEARCH

Convincing follow-up results were needed to be conducted after polypectomy in a statistical manner. In lack of long-term follow-up and sufficient statistical power for clinical application, some details in polypectomy that might lead to recurrence were categorized as complications rather than misdiagnosis or misoperations. Proposed an authorized guidance for either clinicians or patients to direct a regimen and exercise scheme for prophylaxis, which is a hard task that requires plenty of surveys and financial support.

CONCLUSION

This review summarizes the recurrent risk factors for colorectal polyps across four aspects with prophylaxis recommendations.

First, colorectal polyps recur most frequently in male patients, aged >60 years, who are obese and have seldomly accepted NSAIDs. Cigarette and alcohol preference also promote colorectal polyp recurrence. As for genetic variation, a past history of diseases and some polymorphisms are also recurrent factors. Second, proximal growth site along the colorectal wall, three or more polyps with large diameter (≥10 mm), and a great proportion of villous structure of polyps are present in populations at high risk of recurrence. Third, uncomplete polypectomy could delay follow-up surveillance and missed diagnosis would substantially increase the recurrence rate of colorectal polyps. Both the advanced colonoscopy technique and regular surveillance are recommended for patients. A diet that is low in fat and red meat and high in vitamin D, dry beans, fruits, and vegetables (contains flavonols and fiber) may reduce colorectal adenoma recurrence. The principle of our review is to summarize the recurrent risk factors of colorectal polyps as much as possible and predict the tendency of prophylaxis for colorectal polyps even though some risk factors are original and required to be further confirmed.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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