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Non-Alcoholic Fatty Liver Disease as a Risk for Colorectal Cancer Development and the Role of Screening Colonoscopy in Clinical Practice

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Abstract

Colorectal cancer (CRC) is still the third most common cancer in the world, which is the fourth cause of cancer-related mortality. It is caused either due to strong genetic factors such as familial adenomatous polyposis (FAP) and hereditary non-polyposis colon cancer or due to modified metabolic factors such as obesity and diabetes, which represents insulin resistance condition. Non-alcoholic fatty liver disease (NAFLD) is increasing not only in Western countries but also in Asian countries. This disease has been included in the metabolic disease family such as diabetes, hypertension, obesity, and dyslipidemia. Some studies have shown that there is a strong association between NAFLD and the risk of CRC development through the presence of an adenomatous polyp. However, there is currently no consensus on whether routine screening colonoscopy should be done in all NAFLD patients with respects to its cost and invasiveness.

Keywords: Non-Alcoholic Fatty Liver Disease, Colorectal Cancer, Colonoscopy

1. Context

Colorectal cancer (CRC) is still the third most common cancer in the world and it is the fourth cause of cancer-related mortality (1). It is developed from polyp lesions either from adenoma type or hyperplastic type. There are individual risk factors, which are non-modified factors such as genetic, age, and sex. Meanwhile, most CRC cases are thought to be more dependent on lifestyle-related factors (modified factors) such as smoking, meat intake, alcohol consumption, and metabolic factors (diabetes and obesity). Insulin resistance pathway has been considered a major pathway in modified metabolic factor to cause the development of CRC (2, 3).

Non-alcoholic fatty liver disease (NAFLD) is increasing not only in Western countries but also in Asian countries. This disease has been included in the metabolic disease family such as diabetes, hypertension, obesity, and dyslipidemia. This disease spectrum is also based on insulin resistance pathogenesis. Some of NAFLD patients will progress to non-alcoholic steatohepatitis (NASH), and even might further develop liver cancer (hepatocellular carcinoma/HCC) (4-6).

There are studies looking at the association between NAFLD and the development of colonic adenoma where all these studies showed a positive relationship. However, most of the studies only using transabdominal ultrasound for diagnosing fatty liver whereas NAFLD is a wide spectrum of disease, and most of the studies show that NAFLD patients with colonic polyp also possible to have other metabolic diseases (7-9). Therefore, the need for screening colonoscopy in every NAFLD patients need to be carefully considered with respects to the cost-effectiveness.

2. Colorectal Cancer: Pathogenesis, Risk Factors, Screening, and Diagnosis

Gene mutation is the most well-known key player in the CRC development as most of the CRCs arise from the polyps. There are two familial cancer syndromes, which are familial adenomatous polyposis (FAP) and hereditary nonpolyposis colon cancer (HNPCC). In FAP based on natural history, a continuous development of adenomatous polyps occurs because of mendelian autosomal-dominant single gene mutation. In fact, a gene mutation is observed that is located on chromosome 5q. Meanwhile, in HNPCC,

the mutations happened at the repair genes. Cancer usually arises from sessile polyp at the right colon (10). The history of discovery started in 1721 by Menzelio who reported a patient with many colonic polyps and the genetic mutation was first discovered in 1965 by Veale (11, 12). Because of the mismatch of the repair genes and further genetic mutations, it will interfere in the interaction of oncogenes and tumor suppressor genes, which may lead to CRC development. Other clinical syndromes related to the APC gene mutations are attenuated familial adenomatous polyposis, Gardner's syndrome, and Turcot's syndrome (10).

There are already well-known independent risk factors for CRC development such as obesity and diabetes mellitus, where insulin resistance is still the key player in this course of the disease. The insulin resistance mechanism is strongly related to the metabolism process in the liver, muscle, and even in the peripheral tissue. Insulin receptors (IR) which consist of IR-A and IR-B have different impacts in clinical practice. The IR-A found in the fetal tissue whereas IR-B found in the fat tissue, liver, and muscle. In the daily metabolic process, IR-B has the main role for insulin regulation process (13, 14). Obesity as the major source of high free fatty acid (FFA) will interfere the insulin regulation process due to its overload fat accumulation and generated the inflammation process and the activation of NF-κB. Insulin is known as a regulator not only in glucose metabolism but also in lipid homeostasis. The FFA can enter the circulation and taken by the liver or the muscle tissue. This condition could lead to chronic hyperinsulinemia state and insulin resistance. The lipid metabolism is closely related to peroxisome-proliferator-activated receptors (PPAR) gene. The PPAR activation has been studied to find out a possible relationship with CRC development. Another mechanism which has been hypothesized is the COX-2 activation because COX-2 is strongly involved in the oxidative stress due to inflammation process. Insulin itself, through the insulin receptor complex interplay pathway, is the major player in chronic hyperinsulinemia and can promote cancer development (oncogenic signaling cascade). It can induce tumor growth directly through insulin growth factor pathway and also it has an effect on estrogen (15-17). Obesity and type II DM have been strongly related to the increased oxidative stress, which is due to reactive oxygen species (ROS) overexpression. This ROS will trigger P13K/Akt pathway and lead to malignancy. A meta-analysis conducted on 26 studies showed a higher body mass index (BMI) is well-correlated with the risk of CRC development. The relative risk between obesity and CRC development was 1.19 (95% CI, 1.11 - 1.29) (18).

As CRC mostly developed through colonic adenomatous polyp, screening colonoscopy somehow has become a very important tool. However, the cost issue is a big matter when it comes to the screening program in a larger population. Fecal occult blood test (FOBT) is still the most common traditional way used in many countries for possible CRC screening. Even though it is a low-cost, safe, and simple test; however, it has a low specificity, which can be influenced by some foods. This test should be performed routinely. Moreover, it may report false negative results too. Another test such as barium enema has more advantage because more possible polyp or tumors may be detected, even though it still shows less sensitivity in polyps less than 10 mm. The main problem with barium enema is that the polypectomy is not possible to be performed simultaneously. Recent innovation imaging such as CT colonography has become a preferred test in patients who are at risk of perforation but willing to undergo bowel preparation. In some circumstances, this test is still debatable even though it has high sensitivity for adenomas 1 cm because in small polyp detection, the sensitivity is lower than standard diagnostic colonoscopy procedure. Another issue in this test is that the patients also could not undergo polypectomy procedure simultaneously. This kind of test might be better for most patients who already underwent diagnostic colonoscopy procedure without any significant findings and would like to do a general follow-up every 5 years. Flexible sigmoidoscopy has been reported in a randomized controlled trial to be more sensitive in polyp or CRC detection. It has a lower risk and more comfortable for most of the patients due to less bowel preparation; however, it only detects half of the colon part. Capsule colonoscopy also has been approved for screening test; however, it is not effective to detect sessile or serrated polyp lesion. Until now, diagnostic colonoscopy is still the best tool for adenoma or CRC detection (19, 20).

3. Non-Alcoholic Fatty Liver Disease (NAFLD) and Risk of CRC Development

Non-alcoholic fatty liver disease (NAFLD) is a wide spectrum of disease and consists of two phenotypes, which are simple steatosis and steatohepatitis with liver injury. It can lead to more progressive disease and complications such as liver cirrhosis and liver cancer. This spectrum of disease has been well-known as a part of metabolic disease family such as diabetes mellitus, obesity, dyslipidemia, and hypertension. The pathogenesis of NAFLD is mainly based on insulin resistance condition, which obesity and FFA are the main players in this pathway (21, 22)

The study by Fiori et al. (23) indicated the association between liver steatosis with CRC and adenoma in patients with metabolic syndrome (MS) and reported that the incidence of CRC was lower in patients without MS than in patients with MS ($P < 0.05$). Based on further analysis, obesity

and the presence of liver steatosis were independent risk factors for CRC development. Another retrospective study was conducted with larger samples by Bhatt et al. (24) in a 4-year-period on a total number of 591 patients who would undergo liver transplantation (LT) with or without NAFLD. They showed that NAFLD patients were more likely to have polyp than patients without NAFLD (P = 0.04). Interestingly, further multivariate analysis revealed that NAFLD and alcohol consumption were the only significant predictors for polyp development. NAFLD itself is a significant predictor for adenomatous polyp development (OR 1.95, P = 0.02). The study from South Korea by Hwang et al. (25) on 2917 subjects showed that older age, male sex, smoking status, and NAFLD were associated with adenomatous polyp development (OR 2.23; 95% CI, 1.80 - 2.75, OR 1.89; 95% CI, 1.44 - 2.46, OR 1.56; 95% CI, 1.20 - 2.03, and OR 1.28; 95% CI, 1.03 - 1.60, respectively). Previously, a systematic review and meta-analysis were conducted by Shen et al. (9) investigating four cross-sectional and one cohort studies. They revealed that NAFLD was significantly associated with the development of colonic adenomatous polyp (OR 1.74, 95% CI, 1.53-1.97). In China, a similar large retrospective cross-sectional study also showed that the risk for colonic polyp development is increased in men with NAFLD and smoking (26). Study by Yang et al. (27) in Korea showed that colorectal neoplasia occurred more in NAFLD patients during surveillance colonoscopy program (P = 0.008). The COX regression analysis also showed that NAFLD was an independent risk factor for colorectal neoplasm development.

The major drawback from all of these studies is that although NAFLD has a significant association with the risk of CRC development, all adenomas are not considered to be high-risk for CRC development.

4. Non-Alcoholic Fatty Liver Disease (NAFLD) and the Role of Screening Colonoscopy

Until now, there is still no consensus yet about screening colonoscopy in NAFLD patients. There are still major issues which are: (1) Whether NAFLD is the main consideration for screening colonoscopy despite other metabolic factors; (2) simple steatosis or steatohepatitis need to be established before colonoscopy consideration; (3) routine non-invasive tests need to be done in all NAFLD patients to screen which patients need to undergo further diagnostic colonoscopy.

5. Conclusions

CRC is still a major problem which has a strong association with metabolic factors, especially NAFLD. However, the role of routine screening colonoscopy in NAFLD patient in clinical practice is still under debate.

Footnotes

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