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ScienceDirect

Chronic Diseases and Translational Medicine xx (2018) 1–9

www.keaipublishing.com/en/journals/cdtm/

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Perspective

Recent advances in colorectal cancer screening

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Received 26 June 2018

Abstract

Colorectal cancer (CRC) is the third leading cause of cancer-related deaths in the world. Although incidence and mortality related to CRC have declined in the United States largely due to screening, CRC incidence has been increasing in countries that have undergone recent development and industrialization. The past decade has witnessed significant advances in our understanding of molecular pathways in CRC pathogenesis, including conventional adenoma-carcinoma sequence with chromosomal instability, serrated pathway with CpG island methylator phenotype, and microsatellite instability pathway due to mismatch repair deficiency. The increasing availability of multi-gene panel testing provides a promising tool to more precisely stratify patients for their CRC risks. Meanwhile, rapidly accumulating evidence has advanced our knowledge on the efficacy of different screening methods in reducing CRC incidence and mortality. This review aims to provide a concise and evidence-based summary of recent advances in CRC screening.

Keywords: Colorectal cancer; Screening; Colonoscopy

Introduction

Colorectal cancer (CRC) is the third leading cause of cancer-related deaths worldwide.[1] In the United States, 135,430 new cases of CRC were diagnosed in 2017, with 50,260 CRC-related deaths.[2] In the Asia-Pacific region, the incidence varies between regions, with an increasing trend among countries that have undergone rapid development and industrialization. In China, for example, age-standardized incidence of CRC increased from 12.8 in 2003 to 16.8 in 2011 per 100,000 individuals.[3] Timely screening for CRC is critical to reducing CRC-related mortality by detecting the tumor at the early, curable stage. In the United States, large-scale screening programs have led to a significant decrease in CRC morality, highlighting the importance of primary prevention, early detection and treatment.[2,4] Formulating an optimal screening strategy relies upon several important factors, such as local healthcare infrastructure and the availability of medical resources, CRC incidence, the quality of each screening method, and other context-related factors. In

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Peer review under responsibility of Chinese Medical Association.

Production and Hosting by Elsevier on behalf of KeAi

https://doi.org/10.1016/j.cdtm.2018.08.004

this review, we summarize the recent advances in our understanding of CRC pathogenesis and new development in CRC screening.

Colorectal cancer pathogenesis—a heterogeneous disease with different paradigms

CRC, like other types of malignancy, is fundamentally a genetic disease.[5] It is the consequence of the accumulation of deleterious mutations and epigenetic changes, which ultimately lead to uncontrolled proliferation of malignant cells. Over thirty years ago, Fearon et al[6] discovered an important pattern of colorectal carcinogenesis called "adenoma-carcinoma" sequence. (Fig. 1) A predominant feature of this pathway is chromosomal instability with a high percentage of aneuploidy. With accumulation of mutations in genes such as *APC*, *KRAS*, and *p53*, normal colonic mucosa gradually transforms to malignant epithelium in the form of adenomas. This is a multi-step cascade including aberrant crypt foci, low grade dysplasia, high grade dysplasia, and eventually, adenocarcinoma. Because this process typically takes 10 years or longer to complete, screening colonoscopy is recommended every 10 years for average-risk individuals. An exception is the adenomatous polyposis syndromes, characterized by significantly increased number of adenomas in the colon and upper gastrointestinal tract. The most common types of adenomatous polyposis syndromes include familial adenomatous polyposis (FAP) (due to mutations in *APC* gene).[7] FAP is an autosomal dominant condition and accounts for ~1% of all CRC cases. Classical FAP presents with hundreds to thousands of adenomatous polyps throughout the colon and rectum, while attenuated FAP usually presents between 10 and 100 adenomas. CRC screening with colonoscopy should be started at teenage years for FAP patients.[7,8] Prophylactic total colectomy should be considered. Genetic counseling should be provided for at-risk family members.[8]

A different paradigm of colorectal carcinogenesis called "serrated pathway" has been established more recently.[9] The main precursor lesions for the serrated pathway are serrated polyps, particularly sessile serrated adenomas (SSAs, also known as sessile serrated polyps or SSPs). SSA/Ps are predominantly located at the proximal colon and have a flat endoscopic appearance. Histologically, SSA/Ps are characterized by dilatation at the bases of crypts, branched crypts, horizontal extension of crypt bases, or crypts dysmaturation.[10] SSA/Ps frequently harbor *BRAF* mutations and CpG island methylator phenotype, and are responsible for 20%−30% of CRC (Fig. 1).[9,11,12]

Another important cause of CRC is the germline mutations of DNA mismatch repair genes leading to microsatellite instability, a condition called Lynch syndrome (also known as hereditary nonpolyposis CRC, or HNPCC) (Fig. 1).[13] Lynch syndrome is the most common type of hereditary CRC syndromes, representing 2%−4% of all CRC cases. Patients with Lynch Syndrome have up to 80% lifetime risk for CRC and up to 60% risk for endometrial cancer, as well as increased risks for cancers in other organs such as stomach, ovaries, small intestine, hepatobiliary tract,

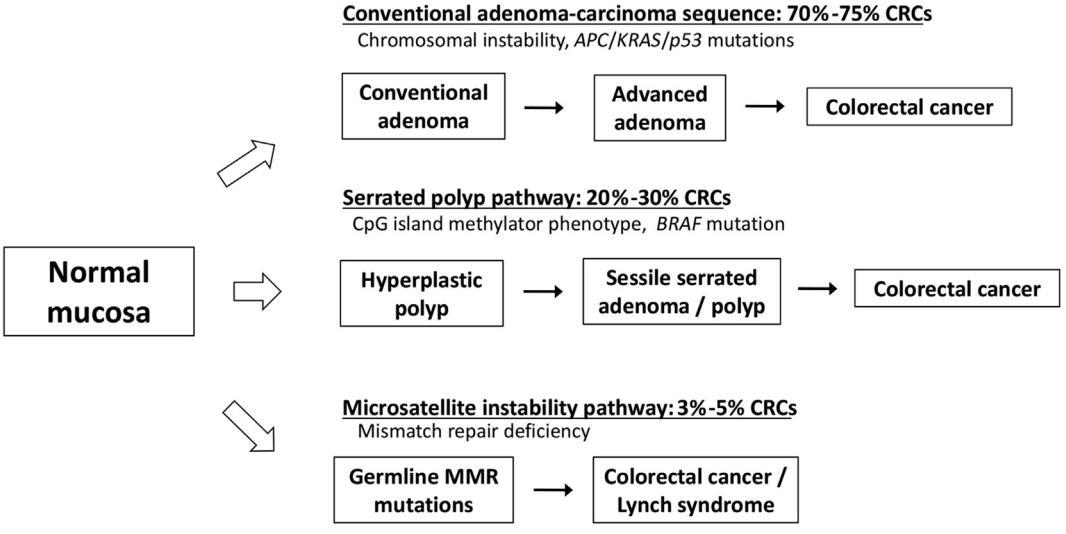

Fig. 1. Main molecular pathways in CRC pathogenesis. CRC: colorectal cancer; MMR: mismatch repair.

Please cite this article in press as: Li D, Recent advances in colorectal cancer screening, Chronic Diseases and Translational Medicine (2018), https://doi.org/10.1016/j.cdtm.2018.08.004