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# Predictive and prognostic biomarkers in colorectal cancer: A systematic review of recent advances and challenges

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ABSTRACT

*Background:* Colorectal cancer (CRC) is one of the leading cause of cancer deaths worldwide. Since CRC is largely asymptomatic until alarm features develop to advanced stages, the implementation of the screening programme is very much essential to reduce cancer incidence and mortality rates. CRC occurs predominantly from accumulation of genetic and epigenetic changes in colon epithelial cells, which later gets transformed into adenocarcinomas.
*Scope of review:* The current challenges of screening paradigm and diagnostic ranges are from semi-invasive methods like colonoscopy to non-invasive stool-based test, have resulted in over-diagnosis and over-treatment of CRC. Hence, new screening initiatives and deep studies are required for early diagnosis of CRC. In this regard, we not only summarise current predictive and prognostic biomarkers with their potential for diagnostic and therapeutic applications, but also describe current limitations, future perspectives and challenges associated with the progression of CRC.
*Major conclusions:* Currently many potential biomarkers have already been successfully translated into clinical practice eg. Fecal haemoglobin, Carcinoembryonic antigen (CEA) and CA19.9, although these are not highly promising diagnostic target for personalized medicine. So there is a critical need for reliable, minimally invasive, highly sensitive and specific genetic markers of an individualised and optimised patient treatment at the earliest disease stage possible.
*General significance:* Identification of a new biomarker, or a set of biomarkers to the development of a valid, and clinical sensible assay that can be served as an alternative tool for early diagnosis of CRC and open up promising new targets in therapeutic intervention strategies.

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## Contents

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## 1. Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed in the world and one of the leading causes of cancer-related death [1]. Colorectal cancer usually develops in the lining of the colon (large intestine) or rectum [2,3]. It has been estimated that nearly 150,000 new cases were diagnosed and 50,000 people died [4] in 2008. In 2012, about 1.3 million new cases has been reported that were diagnosed with CRC and nearly 700,000 patients died of CRC [5]. Recent studies reported that most of the colon cancers start from benign or non-cancerous form, called polyps. If polyps are detected at an early stage and removed from the body, it can prevent the colorectal cancer. Therefore, it is precisely important to identify CRC at an early stage. Although recent studies have reported few molecular biomarkers that can detect CRC at the early stage and also the progression of the diseases Lieu et al. [146], but still there is huge gap which needs to be filled to improve the screening, prevention and treatment of CRC.

Over the last two decades numerous molecular biomarkers for CRC have been extensively studied. There are several screening strategies for detection of CRC which can basically be classified as non-invasive and invasive imaging techniques. But recent studies have also highlighted that they usually lack of proper sensitivity and specificity to screen CRC [6]. Therefore, it is required to study deeply the molecular and genetic aspects in order to find out more reliable and novel biomarkers for the early detection of CRC. Till date, molecular genetics insight studies have found some unfavourable mutations that underlie the pathogenesis of the sporadic and inherited forms of colorectal cancer. Therefore, screening tests are expected to be more sensitive and specific compared to that of currently available screening tests and the validation of the potential biomarker will provide genetic information on the malignancy and metastatic progression. Globally, enormous research efforts have been given at present for identifying molecular markers based on DNA, RNA, or protein to develop novel, non-invasive biomarker detection methods for CRC in blood and stool. Development of colorectal cancer starts due to simultaneous occurrence of multiple biochemical processes which are mediated by genetic mutations, microenvironment factors and epigenetic alterations. While genetic and microenvironment factors have been reported that they have a prevalent role in tumorogenesis, recent studies have showed that epigenetic

**Table 1**
Causes and risk factors for colorectal cancer (CRC).

| | CAUSES AND RISK FACTORS | ACTIVITY |
|---|---|---|
| 1. | Chromosomal instability | Colorectal cancers arise primarily through the chromosomal instability pathway, which is recapitulated by widespread imbalances in chromosome number and loss of heterozygosity and promoting the physical loss of a wild-type copy of a tumour-suppressor gene like APC, P53, and SMAD family member 4 (SMAD4) [10–12]. |
| 2. | Oncogenic mutation of RAS and BRAF genes | Oncogenic mutations are the most common causes to promote CRC carcinogenesis [13]. RAS mutations, in particular KRAS protein has intrinsic GTPase activity, stimulated by GAPs (GTPase activating proteins) activate RAF proteins. B-Raf is a component of MAPK signalling cascade that culminates with activation of several transcription factors important for cell survival, proliferation and metastasis. It has been reported that B-Raf mutations can easily be detected in small polyps compared with RAS mutations, which are common and frequent in hyperplasic polyps, serrated adenomas, and proximal colon cancers [14]. |
| 3. | Adenomatous polyposis coli mutation | The Adenomatous polyposis coli (APC) gene is a tumour suppressor gene that mutated up to 70% of all sporadic colon adenocarcinomas [15,16]. These mutations promotes the activity of other oncogenes such as Wnt, Ras mediated signalling pathway that are needed for neoplastic progression. APC mutations disrupt the association of APC with ß- catenin, outcome in excessive amounts of ß-catenin and over activation of the Wnt signalling pathway [17,18]. |
| 4. | Deleted in Colorectal Cancer (DCC) | DCC was first discovered in a colorectal cancer study during 1990s [19,20]. Recently it is reported that DCC is a tumour suppressor gene. One of the most frequent genetic abnormalities that occur in advanced colorectal cancer is loss of heterozygosity (LOH) of DCC in region 18q21 [21–23]. |
| 5. | Family history | Familial adenomatous polyposis (FAP) is one of the inherited genetic disorders, that enhances the development of several polyps in the colon from a very young age [24,25]. If these polyps are left untreated, they become high risk to develop cancer [26,1]. According to Heavey et al. [27], hereditary nonpolyposis colorectal cancer (HNPCC) seems to accelerate the carcinogenic process through an increased mutation rate in microsatellite regions, which then affects other genes involved in cell cycling and proliferation [28–31]. |
| 6. | Inflammatory bowel disease (IBD) | Regarding IBD, no genetic basis has been identified to explain the predisposition of patients with both Crohn's disease and ulcerative colitis to develop colorectal cancer [32]. Ulcerative colitis drives inflammation of the mucosa of the colon and rectum. Crohn disease enhances inflammation of the full thickness of the bowel wall and may lead towards any part of the digestive tract from the mouth to the anus. Overall these conditions increase an individual's risk of developing colorectal cancer [1,33]. |
| 7. | Smoking | Outcomes from the study of colorectal cancer survivors performed by Cosnes et al. [34], suggested that smoking is associated with a nearly two-fold higher risk of death compared with non-smokers. Further research is needed to investigate the association of smoking with all-cause and CRC-specific mortality among CRC survivors [34–36]. |
| 8. | Age | From epidemiology and clinical research, cancer diverge significantly among different age groups [37]. Colorectal cancer is most commonly occurred at aged over 50 years [38]. The chances of incidence to develop colorectal cancer increases after the age of 40, gradually rises after age 50. It has been reported that much higher prevalence rate is seen at age 60–79 years compared to younger age 40 years [1]; Fatima et al., 2009). |
| 9. | Diet | In the past few decades, it has been reported that intake of many food items and nutrients are associated with the risk of colorectal neoplasia. Diet mainly influences colorectal carcinogenesis through several interacting mechanisms, through the direct effects on immune responsiveness and inflammation, and the indirect effects of over-nutrition and obesity-risk factors for colorectal cancer [1,39–41]. Red meat and processed meat have been found to be associated with an increased risk of CRC [42–44]. Recent studies also revealed that taking of high cholesterol food can increase risk of colorectal cancer [45]. |