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Deciphering Colorectal Cancer Development: From Genomic and Metabolic Perspectives to Innovative Diagnostic Approaches and Nanotechnology-Based Management Strategies

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Aim. To explore the various aspects of colorectal cancer with its correlation with human lifestyles and the inherited genetic makeup and its related metabolism. To understand the various diagnostic patterns, and to explore the nanotechnology-based combined diagnostic and therapeutic methods.
Key points. Colorectal cancer grades as the third most frequently identified malignancy, alongside being the chief cause of cancer related fatalities globally. The modification of normal colonic mucosal lining into a malignant one, as an outcome of collection of many genetic and epigenetic modifications contributes to the colorectal carcinogenesis. However, lifestyle changes have a significant role to play in this. An accumulation of metabolic disorders, the metabolic syndrome, which induces the dysregulation of prime biomolecules are one of the significant factors that induce carcinogenic effects in the normal colonocytes leading to the colorectal carcinogenesis. Non-alcoholic fatty liver disease, also termed as the hepatic expression of metabolic syndrome, is a prime threat for the incidence of colorectal cancer. It induces the malignancy by encouraging secretion of proinflammatory cytokines. As the number of mechanisms leading to colorectal cancer are rising, novel diagnostic tools for the early screening of the cancer are being introduced, and better techniques are still under research. Many studies have indicated the decrease in occurrence and fatalities linked to this disease, which can be attributed to the well-developed screening techniques in cancer management. Nanotechnology, under the area of colorectal cancer management, has improved the screening and delivery of drugs for cancer treatment procedures attributing to its excellent bioimaging and drug encapsulation properties.
Conclusion. This article will review the various genomic and lifestyle interventions affecting the progression of colorectal carcinogenesis. Additionally, we will review the novel and future theranostic techniques available for the management of colorectal cancer.
Keywords: colorectal neoplasms, chromosomal instabilities, non-alcoholic fatty liver disease, metabolic syndrome, cytokines, insulin resistance
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Анализ развития колоректального рака: от геномных и метаболических перспектив до инновационных диагностических подходов и стратегий лечения на основе нанотехнологий

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Цель: изучить различные аспекты колоректального рака, взаимосвязь с образом жизни человека, наследственной генетической структурой и связанным с ней метаболизмом. Понять различные диагностические модели и изучить комбинированные методы диагностики и лечения на основе нанотехнологий.
Основные положения. Колоректальный рак занимает третье место по частоте встречаемости среди злокачественных новообразований, являясь при этом основной причиной смертности от рака во всем мире. Изменение нормальной слизистой оболочки толстой кишки в злокачественную в результате совокупности многочисленных генетических и эпигенетических изменений способствует развитию колоректального канцерогенеза. Однако изменение образа жизни играет в этом значительную роль. Сочетание метаболических нарушений, метаболический синдром, вызывающий дисрегуляцию основных биомолекул, является одним из важных факторов, индуцирующих канцерогенные эффекты в нормальных колоноцитах, что приводит к колоректальному канцерогенезу. Неалкогольная жировая болезнь печени, также называемая печеночным проявлением метаболического синдрома, представляет собой основную угрозу заболеваемости колоректальным раком. Она вызывает злокачественное новообразование, стимулируя секрецию провоспалительных цитокинов. По мере роста числа механизмов, приводящих к колоректальному раку, внедряются новые диагностические инструменты для раннего скрининга рака и продолжаются исследования более совершенных методов. Многочисленные исследования свидетельствуют о снижении заболеваемости и смертности от этой болезни, что можно объяснить хорошо развитыми методами скрининга в лечении рака. Нанотехнологии, применяемые в области лечения колоректального рака, улучшили скрининг и доставку лекарственных препаратов для лечения рака благодаря своим превосходным свойствам биовизуализации и инкапсуляции лекарственных средств.
Заключение. В данной статье рассматриваются различные геномные вмешательства и воздействия, связанные с изменениями образа жизни, влияющие на прогрессирование колоректального канцерогенеза. Кроме того, рассматриваются новые и перспективные тераностические методы, доступные для лечения колоректального рака.
Ключевые слова: колоректальные новообразования, хромосомная нестабильность, неалкогольная жировая болезнь печени, метаболический синдром, цитокины, инсулинорезистентность
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Introduction

Recent studies conducted by National Cancer Institute have demonstrated a novel marked link between the fatty liver diseases and thriving colorectal cancer [1]. Colorectal cancer (CRC) is a prevalent gastrointestinal malignant milieu and is the third chief instigator of cancer correlated fatalities globally [2]. Molecular mechanisms that induce genomic instability, specifically, chromosomal instability, microsatellite instability, CpG island methylator phenotype (CIMP) mediate the pathogenesis of colorectal carcinoma by encouraging tumor development in the colon [3]. Recently, a serrated neoplastic pathway has also been regarded as one of the molecular mechanisms encouraging the growth of colorectal malignancy [4]. Apart from the genetic factors that include aneuploidy, microsatellite instability, gene mutations and gene amplification, epigenetic factors like aberrant methylation of genes, CIMP mechanism, modifications of histone proteins and modifications of chromatin operate rigorously in the active progression of the disease [3, 5]. These genetic pathways mainly function through the disabling of tumor suppressor genes or oncogenes and encourage the lesion growth in the organ [6].

Apart from the genetic and epigenetic pathways, there are a few recognised non-genetic mediators that encourage the tumor microenvironment in the colon. One of the most keenly studied associations is between metabolic syndrome and CRC. Metabolic syndrome, a constellation of various metabolic disorders like increased circumference of waistline, mild to chronic type 2 diabetes mellitus, dyslipidemia, hyperglycaemia, hyperinsulinemia, increased blood pressure (hypertension) and insulin resistance [7, 9]. Caused by sedentary lifestyle, chronic stress, poor dietary habits, smoking and alcohol consumption, metabolic syndrome is said to induce hormonal and systemic changes in the body, leading to the development of cancer [8]. The incidence of the accumulation of these metabolic disorders has increased globally and has been associated with a 13 % increased threat for CRC through many examinations

[7, 9]. Non-alcoholic fatty liver disease (NAFLD) is said to be another independent threat working in the favour of CRC progression [10]. The correlation between them is also influenced by many other factors like metabolic syndrome (MetS), range of inflammation-inducing and inflammation-inhibiting adipokines and cytokines, obesity, age, ethnicity, insulin signaling and other metabolic determinants [10, 11]. This produces a complex mechanism which is still under research [12]. Being one of the prime expressions of MetS, NAFLD is directly linked to the poor glucose metabolism in the body [13]. This in turn links to variations in adipokines and cytokine levels, insulin sensitivity and many other relative factors [14, 15]. All the factors associated with NAFLD have been indicated as independent hazards for CRC, thus leading to the cross-over of these two entities.

Early detection of CRC was found to decrease high death rates associated with it [16]. Importantly, with the emergence of well-programmed CRC screening, the death rates associated with CRC have gradually decreased over the recent decades [17]. Along with the efficient diagnostic techniques, integration of nanotechnology in cancer diagnostics and therapies has grabbed the attention of many in the field [18].

Thus, a lot of research is being funded to understand the various entities that congruously or independently increase the incidence of CRC. The disease was initially known to be influenced by the genetic alterations alone but is now recognized as a complex malignant condition resulting from genomic variations. The genetic abnormalities include many factors leading to genetic instability in an individual [19]. Genomic instability provides a suitable atmosphere for tumorigenesis, which results in the colorectal carcinogenesis. Inflammatory bowel disease, which is regulated by the same genetic abnormalities, also acts as an independent danger factor for the incidence of CRC [20].

Molecular mechanisms influencing the pathogenesis of colorectal cancer

Alteration in serrated pathways are some genetic factors associated with pathogenesis of CRC [3, 21]. The genetic alterations in the oncogenes transform the normal colonic mucosal lining into a malignant one [19]. 75 % of the CRCs arising across the globe are sporadic and are classified into two types: 1) traditional/suppressor/chromosomal instability (CIN) pathway, and 2) mutator/microsatellite instability (MSI) pathway [22]. 70–85 % of the sporadic CRC cases have been found to follow CIN mechanism, while the remaining 15 % of the cases have been found to be mediated through MSI mechanism [19]. Deletion and duplication of genes, and rearrangements of chromosomes mainly in the tumors present in DNA mismatch repair genes are the characteristics of CIN mechanism [19]. The karyotypic abnormalities and accumulation of mutations particularly in genes involved in tumor suppression mechanisms like adenomatous polyposis coli (*APC*), Kirsten rat sarcoma viral oncogene homolog (*KRAS*), tumor protein 53 (*TP53*), B-Raf proto-oncogene (*BRAF*), serine/threonine kinase activate the CRC initiation and progression, and are observed to be a part of the CIN mechanism [3, 6, 19]. Characterized under the umbrella of traditional adeno-carcinoma sequence mechanism, CIN is a homogeneous and distinct pathway [19]. The CIN mechanism is additionally characterized by chromosomal segregation and DNA damage response.

Mutations in repeated short DNA sequences called microsatellites also lead to the progression of CRC which accounts for the MSI molecular mechanism [23]. An examination conducted by F. Jasmine et al. (2021) indicated the strong association of MSI with DNA methylation, thus making it another mediator mechanism for the advancement of colorectal malignancy [23]. MSI mechanism is the molecular fingerprint of mutations occurring in the DNA mismatch repair genes like *MLH1, MSH2, MSH6* or *PMS 2* [6, 24]. The mechanism is driven by the DNA mismatch repair deficiency and is mainly distinguished by frequent sudden alterations at simple nucleotide series [19]. 3 % of the MSI mediated CRCs are associated with Lynch syndrome/non-polyposis CRC syndrome that arises due to the inherited mutations in the afore mentioned mismatch repair genes [4].

Serrated neoplastic pathway is a new mechanism that has been discovered recently and is being studied extensively [4]. The pathway describes the succession of serrated polyps into CRC [4]. Traditional adenomas transform into polyps of serrated type that are a heterogeneous unit of neoplasms and are hyperplastic in nature and are termed as sessile serrated polyps [25]. These are later transformed into malignant adenoma-carcinomic polyps. Mutations in oncogenes like *BRAF* and *KRAS* majorly impact the serrated neoplastic colorectal carcinogenesis [25].

Both CIN and serrated pathways were found to be overlapping with MSI mechanism [25]. The CIMP mechanism is characterized by the hypermethylation of several genes of the CpG island loci and inactivation of genes that suppress tumors [6]. CIMP tumors were found in 30–35 % CRC cases and this mechanism was also found to be overlapping with both serrated and MSI mechanisms [3, 6]. It is a distinct epigenetic mechanism that is majorly detected through the extensive methylation of tumor suppressor genes.

Apart from the biomolecules-induced pathways leading to the growth and advancement of CRC tumors, many novels, external non-genetic factors have been observed to be taking part as independent risk components in the incidence of CRC. However, many studies speculating MetS, a non-genetic factor, to provide an encouraging environment for the proliferation and development of tumor cells, have also

come into light, providing new perceptions of CRC pathogenesis [26].

Metabolic syndrome and colorectal carcinoma

Metabolic syndrome (MetS) is an aggregation of many metabolic disorders like central obesity, hyperglycaemia, hyperinsulinemia, increased blood pressure and dyslipidemia [9, 27]. Influenced by environmental components, genetic variations, sedentary lifestyle, obesity, chronic stress, imbalanced diet, smoking, alcohol consumption and lipodystrophy, the incidence of MetS has significantly increased globally [7–9, 28]. Affecting more than 20 % of the global adult population, it has been found to be prevalent in India, China and the USA [7, 29]. The hormonal and systemic changes triggered by MetS are found to be linked to cancers [8]. Some reports suggest a considerable correlation between the number of MetS factors and increased CRC incidence [7]. High Human Development Index of the well-developed urbanized nations also contributes majorly to the increase in the number of MetS cases, in turn elevating the incidence of CRC by 13 folds [27]. This increase can be attributed to MetS caused by urbanization and sedentary lifestyle [9].

A study conducted by Q. He et al. (2018), with CRC patients, strongly demonstrated that the reduction of occurrence of MetS and its components have the potential to reduce the incidence of CRC by interfering with its pathological manifestations and metastasis simultaneously [30]. An assessment conducted by J.H. Lee et al. (2020), examining incidence of CRC with respect to the ratio of metabolic elements demonstrated a high frequency of CRC in male MetS patients as compared to that of females [29].

Additionally, hyperglycaemia was found to increase colon cell proliferation playing the role of an energy source for colon cancer cells [9]. Increased fecal bile acid concentrations in hyperglycaemic patients also elevated colon transit time inducing colorectal carcinogenesis.

Insulin and colorectal cancer

Many studies have demonstrated the role of increased levels of insulin in the development of colon tumors. Rising levels of insulin also leads to the increase of availability of insulin-like growth factor 1 (IGF-1) [31]. From various studies conducted, it was found that insulin along with IGF take an active part in the development of CRC through their anti-apoptotic and proliferative effect on tumor cells. Many epidemiologic and experimental studies have approved the positive correlation between IGF-1 and CRC mediated by its mitogenic and anti-apoptotic effects [31]. Six insulin-like growth factor binding proteins (IGFBPs) synchronize the activities of IGF-1 [31, 32]. Among them, IGFBP-1 and -2 are inhibited by elevated insulin levels thus leading to the excessive bioavailability of IGF-1 [31]. Insulin resistance, which is a major driving force in the progression of NAFLD, is speculated to be shared as a threatening component by CRC [26]. Additionally, the complex interaction mechanisms of the adipokines and cytokines which lead to proinflammatory host response and insulin signaling dysregulation, are also responsible for the increased risk of CRC [33]. Thus, the

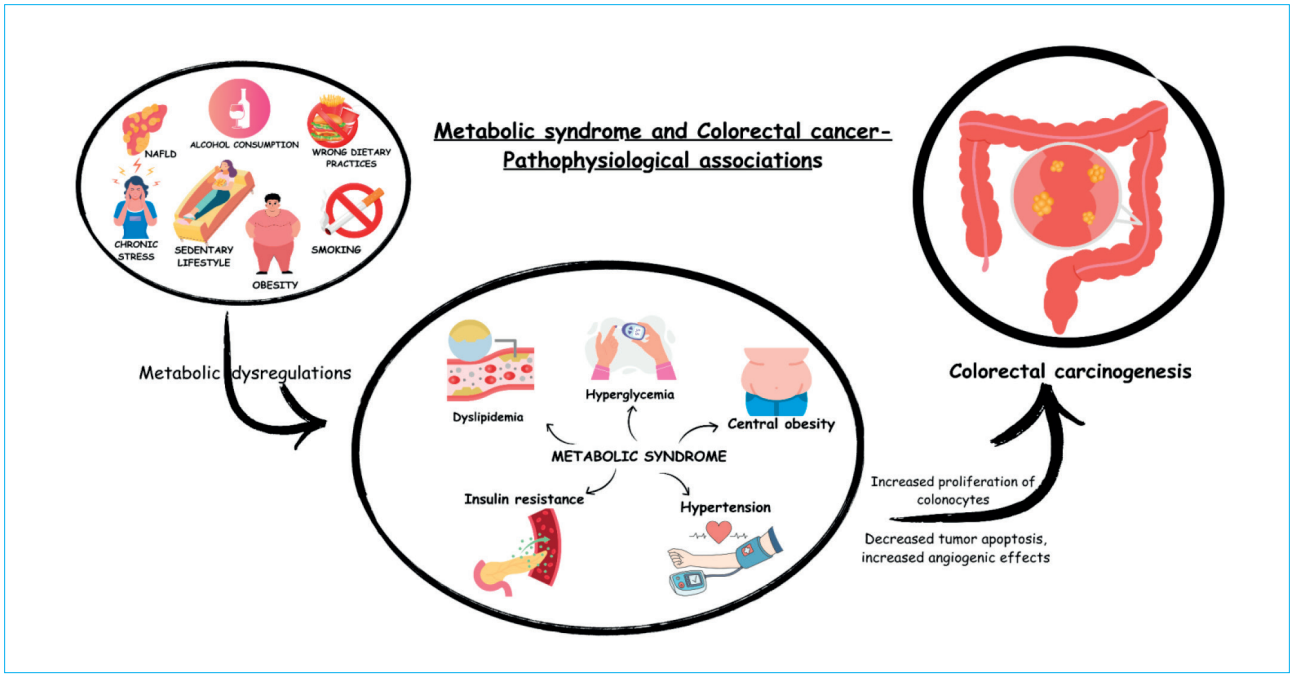

Figure 1. The role of metabolic syndrome in colorectal carcinogenesis
Рисунок 1. Роль метаболического синдрома в колоректальном канцерогенезе

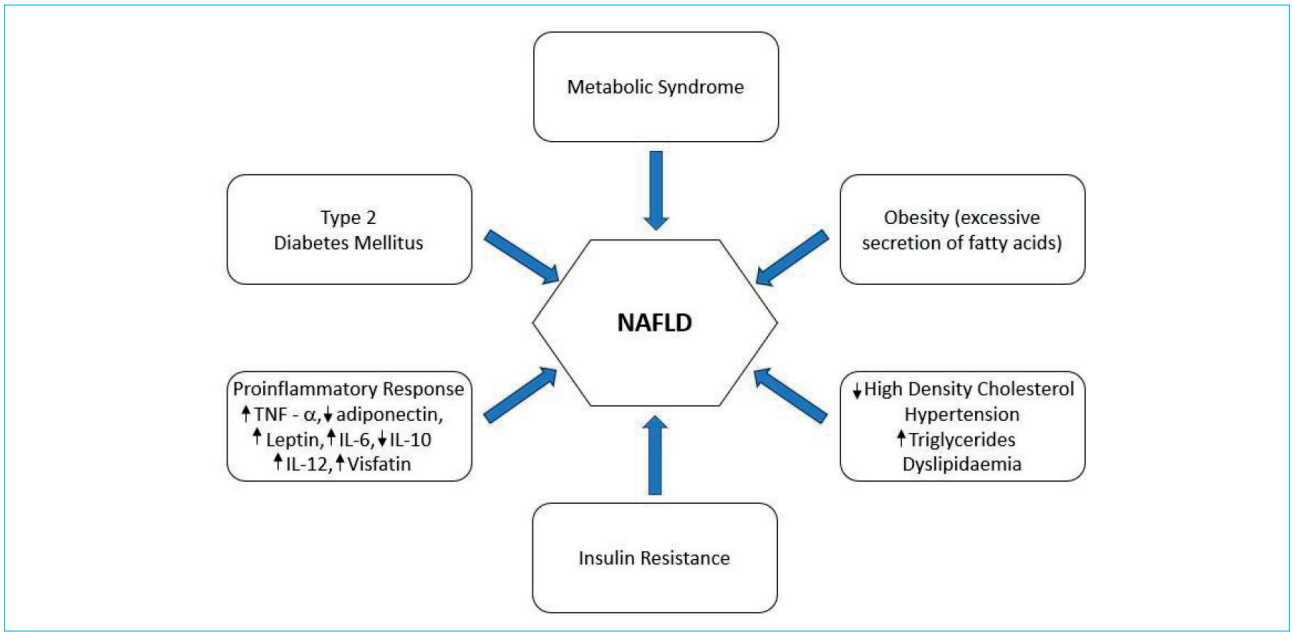

Figure 2. Factors influencing non-alcoholic fatty liver disease
Рисунок 2. Факторы, влияющие на развитие неалкогольной жировой болезни печени

inflammatory cytokine levels are also used extensively as a biomarker to diagnose the incidental risk of CRC [10, 33]. Hence, it is not a surprise that there is some unclear mechanism connecting NAFLD with the incident colorectal cancer.

Non-alcoholic fatty liver disease and colorectal carcinoma

Non-alcoholic fatty liver disease (NAFLD) is commonly defined to be the aggregation of > 5 % hepatic fat per liver mass in the presence of < 10 g of regular ethanol intake and is considered to be an auxiliary feature of MetS with fixed hepatic insulin resistance and inflammatory state [10, 12]. Alteration of metabolic functioning of adipose tissues due to high adiposity caused by obesity leads to excessive secretion of fatty acids, certain hormones and inflammation inducing molecules [11]. The inflammatory host response of NAFLD is influenced by the adipose tissue-secreted bioactive proteins called adipokines and cytokines, namely, adiponectin, resistin, leptin and tumor necrosis factor alpha (TNF-α) [34].

Recent studies provide evidence for the mechanism by which fatty liver diseases promote development of CRC in the liver [1]. Among the various hepatic diseases, NAFLD is proven to be the reason for severe liver damage and malignancies in the gastrointestinal tract and extra-intestinal sites [35]. Apart from being a prime vulnerability for the advancement of hepatocellular cancer, NAFLD has been lately associated a lot with many extra-hepatic cancers like colorectal carcinoma, which is considered as the most repeatedly identified cancer in the globe, and has been ranked the second cause of cancer-linked mortalities in the USA [35].

Many epidemiologic and experimental studies have been performed to confirm the occurrences of the mechanism involved in these associations. The findings of a study concluded that NAFLD could largely influence the succession of metastatic CRC in the liver [36]. Additionally, the study raised a point about different treatment lines for CRC accompanied by NAFLD, and CRC that is accompanied by healthy livers [36].

S. Basyigit et al. (2015) tried examining the negative factors influencing the development of colorectal malignancy in NAFLD patients with reference to insulin resistance in relatively small-scale research. According to the results, the potential for the development of malignancy was significantly linked to the presence of insulin resistance. Furthermore, the incidence of the cancer was severely impacted by the absence of NAFLD. A conclusion was given that the exposure to the cancer was elevated in subjects lacking NAFLD but suffering from insulin resistant conditions [26].

A study conducted by D. Chakraborty et al. (2020), concluded that the pre-existent NAFLD is linked with the limited life expectancy of CRC patients [37]. NAFLD is associated with higher levels of inflammatory response and insulin resistance. A specific milieu occurs because of these conditions that stimulate the advancement of the cancer mediated by the triggering of IGF-1 and hyperinsulinemia [38]. Most of the studies conducted so far have exhibited the independence of presence and increasing threat for CRC from the other expressions of insulin resistance [38].

A meta-study conducted by W. Chen et al. (2020) demonstrated a noticeable positive correlation

between NAFLD and the risk of developing colorectal polyps in the cross-sectional studies with high heterogeneity [39]. However, according to other specific analyses, increased risk of colorectal polyps was linked with NAFLD with relatively lesser heterogeneity. In all, the intensity of NAFLD was not directly linked to CRC, but with the significant vulnerability towards developing colorectal adenomas. The demonstrated correlations were significantly higher in men as compared to women without a lot of heterogeneity. Additionally, the severe inflammatory condition of NAFLD was observed to be the possible mediator of advancement of colorectal polyps and their further succession to CRC [39].

MetS and insulin resistance are linked to the increased vulnerability towards colon cancer; NAFLD, being considered as a hepatic manifestation of MetS and sharing a bidirectional relationship with it, thus gets associated with the elevated threat of colorectal cancer [35]. Insulin resistance is a shared risk factor by both CRC and NAFLD, thus making it another one of the many connecting lines between the two entities [26].

However, owing to the lesser access to better-planned, large-scale prospective analyses with an extended follow-up period, an overall mechanism connecting NAFLD and colorectal cancer remains challenging to be analysed multidimensionally [38]. The results of these studies also demonstrate the importance of CRC diagnosis in cases proven with NAFLD, and the right choice of treatment.

Advancements in diagnostic tools used to analyze colorectal cancer

CRC accounts for 10 % of malignant conditions found worldwide [40]. The gradual collection of genetic and epigenetic modifications results in the development of this cancer from the usual colonic mucosal lining, making it a fatal condition if not treated early [41, 42]. The American Cancer Society predicted that the five-years survival ratio of patients suffering from this disease scales from 90 % if recognised at initial stages, to 14 %, if detected at metastatic stages [43].

European Society of Medical Oncology for Screening proposed a plan for the management of CRC screening and making it more accessible. As per this claim, the adults ranging from 50–74 years, who are at an average risk of CRC should undergo colonoscopy at a regular interval of 10 years in case of a previous negative colonoscopy. Another alternate plan proposed is that the average-risk patients undergo an annual faecal immunochemical test (FIT) with the gap not exceeding 3 years. If the FIT result is found to be positive, a standard colonoscopy is recommended [41]. Although American Cancer Society suggests an annual stool-based screening for patients > 45 years who are at an average risk of CRC, it is recommended to consider it only as a preliminary examination and move forward with the traditional tumor tissue histopathological test [43]. This is due to the unreliability of these tests.

Although there is an appreciable increase in the number of patients participating in these screening programs in recent years, more than half of the population in danger have not acknowledged being tested for CRC [17]. The minimal participation in the screening studies has not helped in bringing down the global CRC statistics till date [44]. The participants mentioned the inefficiency, hazardous outcomes and less accessibility of the existing screening techniques to be the prime factors affecting the minimal participation in screening programs [44].

Among the various diagnostic methods used to identify the disease, American College of Gastroenterology has recommended colonoscopy to be the 'Golden Standard' of colorectal pathology with 99 % specificity for lesions > 6 mm [16, 17, 45]. Despite this, the acceptance of colonoscopy by the population is very low. The major reasons behind this are the specific dietary concerns, bowel cleansing preparation, lack of personalisation, polypectomy bleeding, perforation of the colon, the shame associated with the procedure, miss rate expectancy and 2–6 % CRC risk persistence even after a negative colonoscopy [16, 45, 46].

The traditional tissue biopsies also impose harmful impacts on the individuals and do not represent the tumor heterogeneity; it is difficult to monitor the progression of CRC through the static information that is provided by the traditional biopsies about the tumors [47]. Thus, the existing histopathological tumor tissue analysis which includes colonoscopy and histological examination of tumor is not helpful in forming a personalized treatment for CRC [43].

Observing the hazardous limitations of colonoscopy and the traditional tissue biopsy techniques, other non-invasive diagnostic biomarkers are being used to detect CRC in their early stages [16]. This has influenced the pioneering studies to recognise and isolate various molecular indicators from blood and stool, as new 'personalized biomarkers' for accurate and safer CRC screening examinations [43, 46, 48].

Fecal occult blood test (FOBT) is one of the stool-based, non-invasive and economical CRC screening options [49]. The microscopic blood loss found in the stool, resulting from the progression of CRC can be detected by FOBT [49]. FOBT is of two types — the Guaiac resin-based (gFOBT) and the immunobiological FOBT (iFOBT) [45, 50]. iFOBT is also referred to as FIT [45].

gFOBT, which is not specific to human hemoglobin, is defined as a procedure to assess the pseudo-peroxidase reactivity of haem from hemoglobin molecules found in fecal blood [49]. It is performed with two different stool samples with a specificity exceeding 80 % [45]. It was thus a standard method used to screen CRC [50]. However, since it is unspecific to human hemoglobin, it imposes strict dietary restrictions on the patients undergoing this test [45]. Moreover, its inability to distinguish between

the upper gastrointestinal and lower gastrointestinal tract, false positive results in the presence of ascorbic acid, non-malignant diseases and certain drugs, and the decreased sensitivity for proximal lesions makes it an unreliable source for CRC management [45, 50].

To overcome the shortcomings of gFOBT, iFOBT/FIT evolved. Since the peroxidase catalytic activity is not involved here, there are no dietary restrictions [50]. It detects human globin that's a component of hemoglobin, using specific antibodies [49]. The test is more specific for the bleeding occurring in the upper gastrointestinal tract, as the globin from the upper gastrointestinal tract is digested by proteolytic enzymes [50]. It has a higher sensitivity and specificity to the tumor territory, and a higher sensitisation towards distal colon [45]. Although the sample collection is not very rigorous in FIT, it has to be refrigerated and stored to avoid false negative results [45]. In addition, FIT is not specific to CRC alone as the positive results can also be an outcome of the bleeding caused by non-neoplastic benign tumors [49].

Liquid biopsy is believed to take over the clinical CRC screening in the near future as the method will widely detect tumor-specific changes in carcinogenesis [47]. It is conventionally similar to tissue biopsy and refers to the examination of biomarkers in biofluids like blood, urine and cerebrospinal fluid (usually peripheral blood) [51]. It is a minimally intrusive, real-time technique that employs the isolation of cancer-driving elements like circulating tumor cells (CTC), circulating tumor DNA (ctDNA), miRNA, long non-coding RNAs and proteins from biofluids and conducting their proteogenomic assessments [42, 43]. However, the available data about liquid biopsy has been retrieved from small cohorts [42]. Additionally, the current low-grade standardization of sample collection (ctDNA, CTC, blood) and their isolation, which are against the clinical application of liquid biopsy are under study [42].

Table 1. Efficiency of the diagnostic tools used to screen colorectal cancer
Таблица 1. Эффективность диагностических методов, используемых для скрининга колоректального рака

Management technique	Advantages	Disadvantages	Reference
Colonoscopy	High sensitivity and specificity towards lesions, results in early detection and removal of neoplasms and adenomatous polyps, very reliable with least rate of false positive test results	Invasive, requires extreme manpower, requires specialists and special equipment to perform the procedure, expensive, adherence of patients is required, not personalized	[16, 45, 46]
Tumor-tissue biopsy	Provides information about the molecular profile of the diseased area	Not a real-time procedure, information about the tumor is static and does not provide data regarding the heterogeneity of the tumor, invasive, not reliable, expensive	[43, 47]
Guaiac-based fecal occult blood test (gFOBT)	Standardized, highly sensitive, painless, self-done procedure, economical, non-invasive, detects CRC even before the clinical appearance of it	Patient adherence required, extensive sample collection methods, not specific to human blood and bleeding locations, higher rates of false positive results, chemical interactions with the other components of the procedure itself	[45, 49, 50]
Immunochemical faecal occult blood test (iFOBT) / Faecal immunochemical test (FIT)	Does not require special restrictions being posed on the patients, specific to human blood and bleeding location, simplified methods for sample collection, easily performable, higher sensitivity, economical	Special conditions to store the samples, not specific to clinical CRC, bleeding from non-neoplastic and benign polyps/tumors yields false positive results	[45, 49, 50]
Liquid biopsy	Minimally intrusive, economical, repeatable, real-time method, provides information regarding the tumor heterogeneity, minimum residual disease after surgery, no side-effects, faster turn-around time, monitors chemotherapy resistance of the patient, predicts relapse, personalized diagnosis	No standard method for sample collection, lack of pre-analytical consensus, lack of regulatory support systems, less access to suitable infrastructure, lack of large scale demonstration for clinical applications, higher false positive tests because of accumulation of benign CTC, unclear results in case of lower CTC and cDNA count	[42, 43, 47, 51]

Note: *CRC — colorectal cancer; CTC — circulating tumor cells; cDNA — circulating tumor DNA.*

European Molecular genetics Quality Network (EMQN) observed and calculated circulating tumor DNA identification strategies. They concluded that many analytical and preanalytical variants may produce different results [43]. Additionally, numerous studies have mentioned the absolute need for standardization [43]. The inappreciable infrastructure, undetermined cost, lack of pre-analytical consensus, regulatory support systems, low amounts of ctDNA and CTC in samples, and false positive results are some other reasons that affect the efficiency of this technique [43, 47].

However, it has been evidenced by many studies that the increased amount of ctDNA in an individual's blood is an indicator of the tumor burden the patient is bearing [42]. In addition to this, liquid biopsy is demonstrated to non-invasively present biomolecular profile of CRC with more clarity, as against the traditional tumor tissue biopsy [42]. Alongside providing information about the colonic evolution of CRC and monitoring minimum remainders of the cancer after surgery, liquid biopsy is repeatable and monitors the chemotherapy resistance of the patients [42, 43, 51]. A more nuanced understanding obtained through research will shed light on the efficacy of liquid biopsy in management of CRC [42]. A rigorous plan of action will make liquid biopsy, along with radiological techniques will be the new standard to screen CRC [42].

Health education campaigns, implementation of screening programs and developing personalized medication are some key CRC management factors. In addition to it, the previously mentioned desirable qualities of a screening test should also be met, in order to increase the participation in screening programs [44].

Many studies are being conducted to develop novel strategies that improve the diagnostic efficacy, as well as treatment of CRC. Many stool-based biological markers like RNA and protein-rooted assays are as well-being extensively studied for independent use and for being used as supplements to the previously available tests [44].

Studies targeted at developing new techniques, specifically in the fields of cancer diagnosis and earlier disease treatment have proposed the integration of nanotechnology into CRC management [52]. Nanotechnology has brought about improvement in performances in detection and medical care of CRC and other malignancies by opening doorways to engineering new organized materials [52].

Nanotechnology and colorectal cancer therapy

Nanotechnology is a multidisciplinary field of research that includes the engineering and manufacturing of materials using components of atoms and molecules [18]. Nanotechnology has been integrated with CRC management in the following ways: 1) distinct detection of tumors and malignant biomarkers; 2) nanoparticles-based biologically targeted contrast agents; 3) nanoparticle drug carriers [17, 52, 53]. Nanomaterials have astonishingly been evidenced to diagnose and treat CRC simultaneously and are said to possess theranostic potential [53]. Nanoparticles (NPs) are also termed as 'nano vehicles' and 'nano carriers' for the same reason [54, 55].

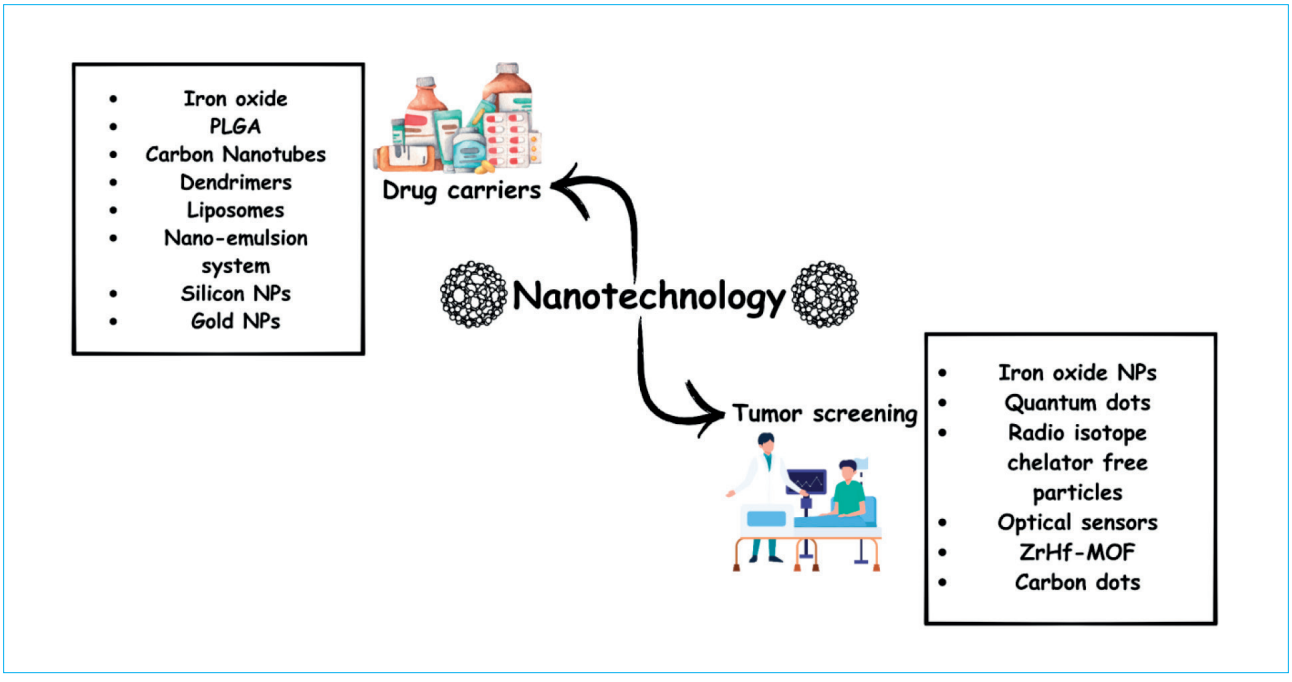

Figure 3. Uses of nanotechnology in colorectal cancer management
Рисунок 3. Использование нанотехнологий в лечении колоректального рака

Currently, carbon nanotubes (CNTs), manufactured dendrimers, modified liposomes, silica nanoparticles (SiNPs), gold nanoparticles (AuNPs), metal-organic framework (MOFs), core-shell polymeric nano-formulations (CSPNFs), nano emulsion system are some crucial steps of nanotechnology towards CRC management [53].

Molecular and cellular imaging, which is a crucial part of diagnosis and treatment, can be achieved in precision and real-time, using NPs [56–58]. Prime imaging procedures, particularly magnetic resonance imaging (MRI), positron emission tomography (PET) and optical imaging, used for cancer theranostic fields have been significantly enhanced by the use of NPs [56].

Quantum dots (QD) based interleaved molecular level imaging procedures determine the temporal-spatial relationship among molecules by parallelly pigmenting malignant bioindicators [59, 60]. It helps in decoding the molecular pathways of cancer progression and investigating the tumor microenvironment [59]. When conjugated with biomolecular agents like antibodies, peptides and smaller molecules, QDs target cancer cells with elevated specificity [59]. However, the extreme cytotoxicity that accompanied QD usage has been demonstrated to be overcome by the development of optical sensors [57]. Optical sensors make use of various imaging nanoprobes and are actively being developed for the treatment of cancer [57]. Advanced and sensitized identification of malignant bioindicators and live oncocytes is also promised by metal-organic frameworks like ZrHf-MOF [61]. NPs like carbon dots planted within the intramural voids of ZrHf-MOF increase the biocompatibility, fluorescence and electrochemical activity of the recently developed aptasensor, making it a crucial leap in the field of 'Cancer management and nanotechnology' [61]. Many new NPs are being synthesized by integrating diverse effective components to enable multi-sensory imaging and therapeutic procedures simultaneously [58].

In addition, NPs are used in multifunctional cancer therapies [62]. When given intravenously, they excavate into tumor tissue and accumulate there and are eventually infiltrated to the tumor sites [59]. Ionic strength, magnetic field and temperature are factors that stimulate NP drug delivery and controlled release [62]. Iron(III)oxide (Fe_3O_4) has appreciable surface modification and self-assembly capabilities, drug encapsulation and remote-controlled drug release mechanism [62]. Iron(III)oxide filled NPs increase the magnetic hyperthermic effect, that induces DNA damage and compromises tumor cells, and helps in the killing of CRC cells, alongside facilitating MRI for biological responses to anti-cancer therapies [62, 63]. Biodegradable polylactide-co-glycide (PLGA) NP is also a nano drug carrier which is evidenced to prevent drug degradation, sustained drug release and facilitate intracellular delivery of bioactive materials [59, 64]. PLGA nanoparticles fail to distinguish cell types, and this limitation is overcome by tagging it with suitable ligands, making it an approved biodegradable polymeric NP (PNP) [59, 64]. PNPs are known for outstanding endocytosis proficiency, apathetic tumor targeting and high encapsulation competency, making them prolong the action of the drug in the host, increase the solubility of the drug and enhance permeability of tumor cells towards drugs [64]. Thus, they are used to overcome certain physicochemical limitations of natural anticancer drugs/reagents [64].

Carbon nanotubes are also highly researched nano carriers. Single walled carbon nanotubes with higher surface area, increased aspect ratio and unique cylindrical structure similar to biological tubular structures, along with unique optical, thermal and electrical properties, increase the effect of hyperthermia in tumor sites and thus, kill tumor cells [65, 66].

Dendrimers are one of the important macromolecular nanoscale drug delivery devices [67]. Dendrimers are radially symmetrical, hyperbranched artificial macromolecules used in anti-cancer theranostic applications [67]. An investigation evidenced appreciable results regarding the excellent capturing and downregulation of CTCs by nano drug vehicles when dendrimers were functionalized by coating them with two antibodies as against their single antibody counterparts [68]. It also provided conceptual evidence about the possibility of conjugating two antibodies with nanoparticles to encapsulate and downregulate CTCs in the body, which amplified the specificity of these vectors, thus demonstrating the efficiency of nanoparticles in cancer theranostic applications [68].

Stealth/modified liposomes are another class of nano drug carriers [69]. Natural liposomes present in our body are capable of carrying drugs safely to specific sites and have excellent compatibility with various cell membranes [69]. However, their half-life and applications are limited *in vivo*, due to the reticuloendothelial system which encapsulates them [69]. This can be overcome by coating the outer layer of liposomes with hydrophobic polymers like polyethylene glycol (PEG). This increases their half-life and directs them to certain specified organs, making them efficient anti-cancer drug carriers [69].

Nano emulsion system is a mixture of water, oil and surfactant, which is thermodynamically uniform, physically stable and minimally stable, and can facilitate the transfer of drugs with high security against heat and extreme pH of the host body [18, 70]. It is also one of the most studied nano formulations for anti-cancer drug transfer. Silica nanocrystals, obtained from photoluminescent porous silicon, are excellent drug delivery agents that escape renal filtration for prolonged residence in the host body [71]. They are evidenced for controlled release of drugs [71]. Gold nanoparticles (AuNPs), utilized in the active and passive delivery of biomolecules to target organs are the most stable nano drug carriers [55,

72]. With an excellent X-ray absorption index and region-confined surface plasmon resonance radioactivity, they are outstanding anti-cancer therapeutic components and vectors for imaging factors and delivery of drugs [55]. By alleviating the solid stress in tumors and enhancing the tumor vessel perfusion and oxygen delivery, AuNPs decrease hypoxia and sensitize therapy of anti-cancer drugs like cisplatin [72, 73].

Apart from the common NPs, keen attention is being paid to nano combinatorial medicine which is the combination of nanomedicines a cancer patient is exposed to, for theranostic purposes. Although more work needs to be done on the synergistic drug combinations, dosage ratios and nano carrier compatibility, the significant therapeutic effect, minimal toxicity, improved pharmacokinetic profiles of cancer patients and excellent encapsulation of drugs mechanism of the nano combinatorial medicine technology have made many companies translate them from lab bench to clinical trials [73, 74].

Nanotechnology has helped overcome the long-term invasive side-effects of the regular CRC diagnostic tools and chemotherapy techniques in many ways. Many ongoing research studies are also demonstrating the positive effects of the use of NPs for cancer management and a peek into the future perspectives of nanotechnology in the biomedical field.

Conclusion

CRC is the most meticulously identified cancer cluster around the globe. With over a million cases being reported every year, CRC is linked to significantly elevated fatality rates. It is considered to be a complex disease, developed because of the accumulation of many endogenous and exogenous factors. Several genetic pathways have been determined for the pathogenesis of CRC. NAFLD, regarded as a hepatic expression of MetS, is a novelly discovered, one of the few exogenous factors controlling the pathogenesis of CRC. NAFLD, distinguished by varying levels of cytokines and adipokines with proinflammatory effects, increased insulin resistance, malfunctioning of the hormone insulin, and obesity, has been interlinked to the advancement of CRC through the same elements. The alarming rise in the obese population, type 2 diabetes mellitus cases, and the number of MetS cases is predominantly linked to the rise in NAFLD cases which eventually gets associated with the elevated incidence of CRC. Thus, it becomes important to detect and attend to CRC in the early stages of the disease. Many diagnostic tools like colonoscopy and tumor tissue biopsy are invasive and impact the patients adversely over a long time. Older techniques like tumor tissue biopsy, along with the newly discovered strategies like liquid biopsy and FIT, prove to be the most promising set of diagnostic tools to manage CRC, each having major advantages, one over the other. Chemotherapies and other cancer therapy have invasive side effects on the patients. Thus, nanotechnology, which includes the engineering of biocompatible nanoparticles, is being studied extensively for its application in cancer therapy. NPs have overcome many challenges like static tissue imaging and inefficient drug infiltration

Table 2. Applications of nanoparticles in various fields of cancer theranostic effect
Таблица 2. Применение наночастиц в различных областях тераностического эффекта при лечении рака

Nanoparticles in CRC management	Advantages of these applications in CRC management	Constituents of the technology	Reference
Imaging nanoprobes	Improved contrast for imaging, multimodal, multifunctional, molecular and cellular level imaging along with simultaneous staining, significant specificity and enhanced fluorescence imaging	· Iron oxide NPs · Quantum dots · Radio-isotopic chelator free particles · Optical sensors · ZrHf-MOF · Carbon dots	[56–61]
Nano drug carriers	Specific to tumor tissues, hyperthermic killing of tumor cells, non-invasive, efficient drug encapsulation, amplifying drug efficacy, increased cellular endocytosis efficiency, cell sensitisation towards drugs, controlled delivery of drug and molecular sensing	· Iron oxide NPs · Carbon nanotubes · Dendrimers · Modified liposomes · Nano-emulsion system · Silicon NPs · Gold NPs	[18, 55, 59, 62–72]
Combinatorial medicines	Targeted drug delivery, therapy and diagnostic applications, minimal cytotoxicity and improved pharmacokinetic profiles of cancer patients	Dosage ratio and analysis of components of drugs under research	[73, 74]

Note: *CRC — colorectal cancer; NPs — nanoparticles; ZrHf-MOF — zirconium and hafnium based metal-organic framework.*

and proven to be excellent bioimaging probes and drug carriers, thus implying that they can be used for diagnosis and treatment purposes simultaneously (theranostic purposes). Quantum dot NPs, Silica NPs, AuNPs, PNPs, stealth liposomes, metal-organic frameworks and nano combinatorial medicine are some of the crucial achievements of nanotechnology that have gotten it closer to cancer management. They have been studied and proven to be good nano vehicles to carry drugs safely and specifically to the tumor sites of the tissue along with emitting a good amount of fluorescence for bioimaging purposes. All the recent developments in the diagnostic and therapeutic tools of CRC have significantly reduced the occurrence and temporality associated with the condition, thus taking today's world towards a healthier future.

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