

REVIEW

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# The role of physical activity and epigenetic changes in colorectal cancer prevention

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## Abstract

Regular and consistent physical activity significantly reduces the risk of colorectal cancer (CRC) by approximately 24% in men and 23% in women. There are several mechanisms through which exercise can help protect against CRC. For example, it can reduce chronic inflammation, boost the immune system, and cause positive epigenetic changes like DNA methylation and histone modifications. It increases the activity of immune cells like natural killer cells and cytotoxic T lymphocytes, shifts macrophages to an anti-tumor state, and promotes a tumor-suppressive microenvironment. Exercise also positively affects the gut microbiome, increasing beneficial bacteria that produce anti-inflammatory short-chain fatty acids like butyrate, which strengthen gut health and support epigenetic regulation. Additionally, physical activity lowers oxidative stress, enhances DNA repair, and regulates hormones like insulin and IGF-1, which are associated with cancer progression. Although exercise benefits vary among individuals, especially between genders, it is still a powerful preventive and therapeutic tool for CRC. For patients and survivors, personalized exercise programs improve physical function, decrease fatigue, and improve overall quality of life. Overall, exercise offers a multifaceted approach to CRC prevention and management by targeting inflammation, immunity, epigenetics, and gut health, as this review explores.

**Keywords** Physical activity, Epigenetic changes, Colorectal cancer, Inflammation, Immunity

## Introduction

Colorectal cancer (CRC) is a prevalent cancer worldwide, significantly impacting public health due to its high occurrence and mortality rates. Notably, lifestyle factors, such as diet and physical activity, significantly influence CRC risk. Epidemiological studies indicate that regular exercise can reduce the risk of CRC by approximately 24% in men and 23% in women, emphasizing the

importance of physical activity as a preventive strategy. Furthermore, the increasing incidence of early-onset colorectal cancer (EOCRC) in younger populations raises important questions about lifestyle and genetic factors that may be contributing [1, 2]. Exercise protects against CRC through several biological mechanisms, including reducing inflammation, improving immune function, and promoting beneficial epigenetic changes. Regular physical activity lowers levels of pro-inflammatory markers and interferes with signaling pathways that encourage cancer cell growth. Additionally, exercise can affect epigenetic modifications, such as DNA methylation and histone modifications, which are important in controlling gene expression related to cancer development. These changes not only decrease cancer risk but may also enhance treatment outcomes for CRC patients, highlighting the diverse benefits of physical activity [3,

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4]. Although there is agreement on the positive impact of exercise, its effectiveness varies, especially among different groups like women, where protective effects may be less significant [5]. Additionally, the interaction between genetic predisposition and lifestyle factors, including the gut microbiome, makes understanding CRC risk more complex [6, 7]. Recent research highlights the importance of individual differences in response to exercise, suggesting a need for tailored exercise recommendations that consider one's health and genetic background [8]. The growing field of epigenetics further emphasizes the importance of lifestyle changes, including exercise, in preventing CRC. Epigenetic alterations, which do not change the DNA sequence but affect gene expression, can be influenced by physical activity, showing how lifestyle can change cancer risk. As research advances, the relationship between exercise, epigenetics, and CRC prevention remains important, providing new insights into potential interventions and health strategies for reducing CRC incidence [3, 9, 10].

### Colorectal cancer epidemiology

CRC is still a major health concern worldwide, with significant differences in incidence and mortality between men and women. In the United States, about 2,041,910 new cancer cases are expected in 2025, with CRC being a major contributor [1, 2]. Historically, men have had higher CRC incidence rates than women [2]. Data from 2015 to 2019 show that the age-standardized CRC incidence rate was 33% higher in men (41.5 per 100,000) compared to women (31.2 per 100,000). This difference is due to variations in risk factors, such as higher rates of excess body weight and processed meat consumption among men [2]. Worldwide, the incidence of CRC is higher in men than in women, and this trend is expected to continue. In 2022, men had a higher incidence and greater number of deaths from CRC than women, and this disparity is expected to increase by up to 16% by 2050 [11]. Recently, there has been an increase in early-onset colorectal cancer (EOCRC), which occurs in individuals under the age of 50. This trend is concerning because, compared to late-onset colorectal cancer (LOCRC), EOCRC tends to be more aggressive and diagnosed at later stages. Several factors contribute to the rise of EOCRC, including an increase in obesity and poor dietary habits across generations. Additionally, genetic factors play a significant role, with approximately 30% of EOCRC cases attributed to inherited mutations, compared to about 15% in LOCRC [12]. CRC is influenced by a combination of genetic, epigenetic, and environmental factors. Lifestyle choices, particularly diet and physical activity, can significantly affect the onset of CRC. Epidemiological studies show that regular physical activity is associated with a reduction in CRC risk. Evidence

suggests a risk reduction of approximately 24% in men and 23% in women [13].

### Physical activity and risk reduction

Physical activity plays a crucial role in reducing CRC risk, with different activity levels categorized by their metabolic equivalent (MET) values [14]. Light-intensity activities, ranging from 1.6 to 2.9 METs, include standing, casual walking, and household chores. While these activities require minimal energy and may not independently offer significant CRC protection, they contribute to overall physical activity [3, 15]. Moderate-intensity activities, ranging from 3.0 to 5.9 METs, include brisk walking, gardening, and recreational activities like golf [16]. These activities require moderate effort and are associated with numerous health benefits, including improved cardiovascular and metabolic health. Studies suggest that moderate physical activity can contribute to reduced CRC risk by improving digestion, reducing inflammation, and regulating body weight, a key factor in cancer prevention [4, 17]. Vigorous-intensity activities, classified as 6.0 METs or higher, include high-energy exercises like running, swimming, and squash or racquetball. These activities require significant effort and have demonstrated even greater protective effects against CRC. These high-intensity activities help regulate hormones like insulin and insulin-like growth factors, implicated in cancer development. They also enhance immune function and reduce systemic inflammation, creating an environment less conducive to cancer cell proliferation [3, 14]. Despite the clear benefits of physical activity in reducing CRC risk, research indicates that protective effects are more variable among women than men [8]. The reasons for this inconsistency remain unclear, although hypotheses suggest that hormonal differences, variations in fat distribution, and lifestyle differences may contribute [18]. Further studies are needed to determine how exercise frequency, intensity, and individual metabolic responses influence gender-based differences in CRC risk reduction through physical activity [18, 19].

### Dietary factors

Diet plays a significant role in CRC risk. A diet rich in vegetables, fruits, and whole grains is consistently linked to a lower risk of CRC. These foods are high in fiber, antioxidants, vitamins, and minerals, which promote overall health and may protect the colon from cancer-causing substances. Fiber promotes healthy digestion and regular bowel movements, potentially reducing the time carcinogens are in contact with the colon lining [20–22]. Conversely, a high intake of red and processed meats is associated with increased CRC risk. Red meats (beef, pork, lamb) and processed meats (sausages, bacon, hot dogs) contain cancer-promoting substances. These

include heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs) formed during cooking, which can damage DNA and cause cancerous changes in cells. Processed meats often contain preservatives like nitrates, which can be converted into carcinogenic nitrosamines [20, 23–25]. Maintaining a healthy weight is crucial for reducing CRC risk. Overweight and obesity increase the likelihood of CRC. Excess body fat, especially abdominal fat, can elevate insulin and insulin-like growth factors (IGFs), implicated in cancer development and progression. Obesity is also linked to chronic inflammation, fostering an environment conducive to cancer cell growth. A balanced diet and regular physical activity are crucial for maintaining a healthy weight and preventing CRC [20, 26].

#### **Early-onset colorectal cancer (EOCRC)**

Recently, there has been a concerning increase in early-onset colorectal cancer (EOCRC) cases, particularly among individuals under 50 years. This rise is concerning, as CRC has traditionally been more prevalent in individuals over the age of 50. EOCRC differs from late-onset colorectal cancer (LOCRC) in significant areas, including its epidemiological, pathological, and biological characteristics. For instance, EOCRC tends to be more aggressive and is often diagnosed at a more advanced stage, making it more challenging to treat. The biological mechanisms underlying EOCRC may also differ, involving distinct genetic mutations and alterations compared to LOCRC [2, 20]. Several factors contribute to the increase in EOCRC cases. A major factor is the rising rates of obesity and higher body mass index (BMI) among younger populations. Obesity has been strongly linked to the development of colorectal cancer, as excess body fat can lead to hormonal changes, inflammation, and other metabolic disruptions that can increase cancer risk. Poor dietary habits, such as high consumption of processed foods and red meat, and low fiber intake, also contribute to the increased risk of EOCRC, along with obesity. These poor-quality diets can disrupt normal colon function and promote cancerous growth [20, 27, 28]. The gut microbiome, comprising trillions of bacteria and other microorganisms in the digestive system, has also been identified as a potential factor in EOCRC development. Research has shown that changes in the gut microbiome, influenced by diet, lifestyle, and other environmental factors, can play a role in cancer development. A dysregulated microbiome can lead to inflammation and the production of carcinogenic substances, increasing colorectal cancer risk [29, 30]. Genetic and hereditary factors also contribute to the rise of EOCRC, although they account for a smaller proportion of cases. Approximately 30% of EOCRC cases are linked to genetic factors, compared to about 15% of LOCRC cases. These genetic factors include

inherited mutations in specific genes that predispose individuals to CRC, such as in familial adenomatous polyposis (FAP) or Lynch syndrome. Family history plays a significant role in determining the likelihood of developing EOCRC, with individuals who have relatives with early-onset CRC at a higher risk. The increasing prevalence of EOCRC highlights the need for further research to understand the interplay of genetic, environmental, and lifestyle factors and to identify prevention and early detection strategies for younger populations [20, 31–33].

#### **Genetic and epigenetic factors**

At a molecular level, CRC development results from complex interactions between genetic mutations and epigenetic modifications. Inherited mutations in genes such as Adenomatous Polyposis Coli (APC) and MutL Homolog 1 (MLH1) can predispose individuals to CRC. Additionally, environmental exposures, such as chemicals and lifestyle factors, can induce mutations in these critical genes, along with chromosomal abnormalities and epigenetic changes that silence tumor suppressor genes, thereby facilitating tumorigenesis. The interplay of these factors highlights the importance of lifestyle modifications, including regular exercise and dietary improvements, in CRC prevention and management [20, 34–36].

#### **Exercise and its effects**

##### **Exercise's role in CRC through altering the body's inflammatory response**

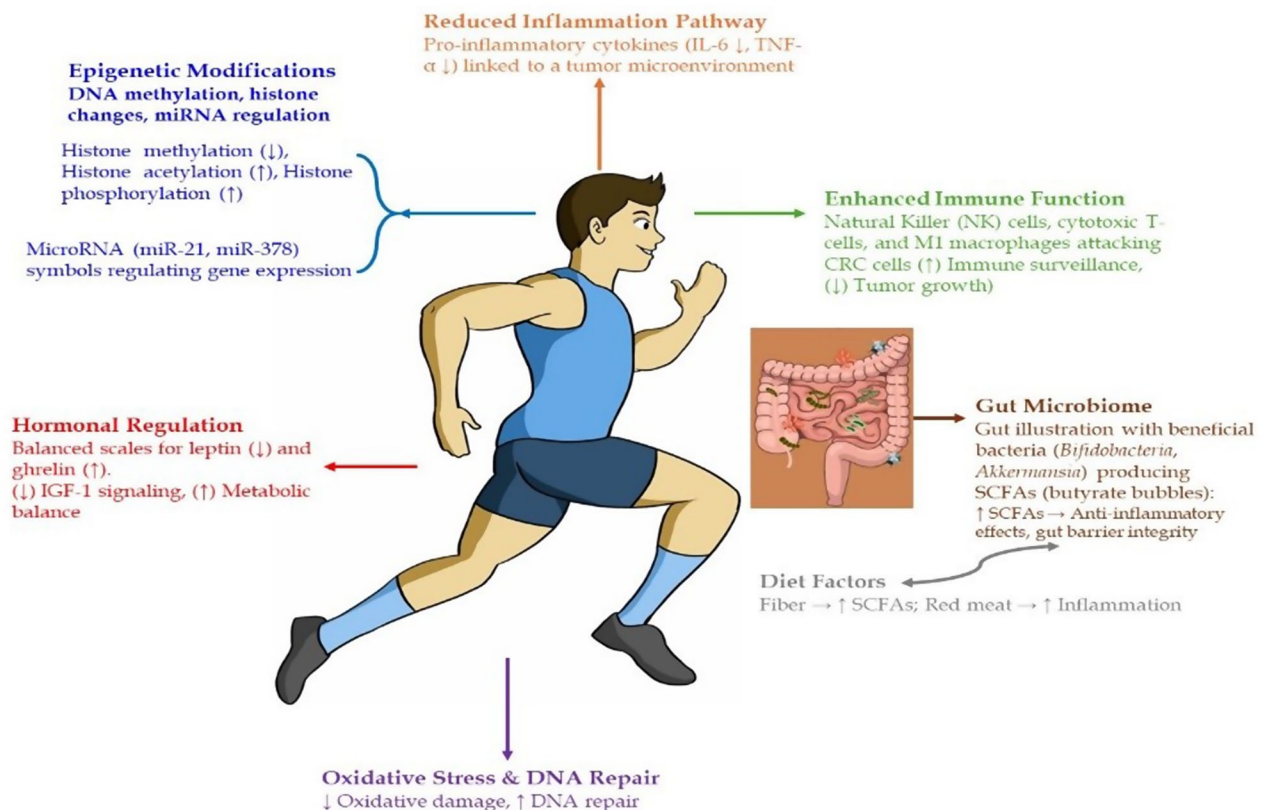
Exercise plays a significant role in CRC prevention and management by influencing several biological mechanisms at the cellular and molecular levels. One of the most important ways in which exercise reduces CRC risk is by altering the body's inflammatory response. Chronic inflammation is well-documented as a key factor in the development and progression of various cancers, including CRC. Prolonged inflammation leads to elevated levels of pro-inflammatory molecules, including cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- $\alpha$ ). These molecules are involved in a range of processes that can facilitate tumor formation and progression. For instance, they can promote cancer cell survival, encourage abnormal cell division, and stimulate angiogenesis, which is critical for tumor growth [37–41]. Exercise has been shown to reduce the levels of these pro-inflammatory cytokines, thus helping to prevent the chronic inflammatory state that could contribute to cancer development. Regular physical activity shifts the balance from high to low inflammation. This reduction in inflammation is crucial because inflammatory molecules like IL-6 and TNF- $\alpha$  are involved in multiple stages of cancer progression. IL-6, for example, can directly influence the proliferation and survival of cancer cells, while TNF- $\alpha$  is associated with tumor invasion

and metastasis (the spread of cancer cells to other parts of the body). By lowering the concentrations of these molecules, exercise creates an internal environment less favorable for CRC cell initiation and spread. This means physical activity may reduce the risk of tumorigenesis, the process by which normal cells become cancerous, and the ability of cancer cells to spread or grow uncontrollably [3, 42–45]. Overall, by mitigating chronic inflammation, exercise reduces the activity of molecular pathways that contribute to cancer progression, making it a powerful preventive tool against CRC. Additionally, this anti-inflammatory effect may also help prevent cancer recurrence in individuals who have already been diagnosed and treated for CRC. Therefore, regular physical activity significantly contributes to cancer prevention by disrupting the inflammation cycle associated with tumor development and metastasis (Fig. 1) [3, 46].

#### Effect of exercise on COX-2 expression and CRC

In CRC, COX-2 is frequently overexpressed during early tumor development, making it a critical factor in CRC initiation and progression. This overexpression is associated with increased PGE2 production, which activates several downstream signaling pathways, including the Wnt/ $\beta$ -catenin pathway, crucial for CRC development.

Upon activation,  $\beta$ -catenin translocates to the nucleus, triggering the expression of genes that promote cell proliferation and survival [47, 48]. COX-2-derived prostaglandins can increase  $\beta$ -catenin stability and enhance its transcriptional activity. They can also activate NF- $\kappa$ B, a transcription factor crucial for inflammation and immune response. NF- $\kappa$ B activation leads to the expression of genes involved in cell survival, inflammation, and metastasis, all of which are beneficial to tumor growth [49, 50]. Prostaglandins, particularly PGE2, can activate the PI3K/Akt signaling pathway, which regulates cell survival, metabolism, and growth. This pathway is frequently dysregulated in cancer, and its activation by COX-2 contributes to cancer cell survival and proliferation [50, 51]. Exercise can influence tumor development by affecting COX-2 expression, an enzyme crucial for inflammation and cancer progression. During physical activity, the body undergoes physiological changes that help reduce systemic inflammation, a key driver of cancer. Exercise triggers a reduction in pro-inflammatory cytokines, molecules that promote inflammation. These cytokines, such as TNF- $\alpha$ , IL-1 $\beta$ , and IL-6, upregulate COX-2. Reducing these inflammatory signals through exercise lowers COX-2 expression, ultimately decreasing the production of prostaglandins like PGE2, which are critical for tumor



**Fig. 1** Summary of the importance of physical activity in colorectal cancer prevention and management

growth [3, 52, 53]. In addition to reducing cytokines, exercise stimulates the release of anti-inflammatory proteins, such as IL-10 and heat shock proteins. These proteins counteract inflammation and modulate the immune response. IL-10, for example, inhibits NF- $\kappa$ B activation, a transcription factor that promotes COX-2 expression and other inflammatory processes. By reducing NF- $\kappa$ B activation, exercise further suppresses COX-2 production and inflammation [54, 55]. Moreover, during exercise, increased cellular energy demand activates AMP-activated protein kinase (AMPK). AMPK regulates cellular metabolism and has anti-inflammatory properties. It inhibits COX-2 expression in various tissues, including the colon, by downregulating inflammatory pathways such as NF- $\kappa$ B. This AMPK-mediated COX-2 inhibition is another important way exercise may reduce tumorigenesis [56–58]. Exercise can also affect gene expression through microRNA regulation. MicroRNAs are small

non-coding RNAs that regulate the translation of specific genes. Some microRNAs, such as miR-101, directly target and reduce COX-2 expression by binding to its messenger RNA, leading to degradation. These exercise-driven molecular changes significantly impact COX-2 reduction and, consequently, the inflammatory environment that supports cancer development [59–61]. By modulating these pathways and reducing COX-2 expression, exercise lowers pro-inflammatory molecules that fuel cancer growth. This creates a less favorable environment for tumor formation and reduces cancer progression. Overall, exercise powerfully modulates molecular and cellular mechanisms involved in tumorigenesis, providing a protective effect against cancer by targeting COX-2 and inflammatory processes [54] (Table 1).

**Table 1** Some important studies related to physical activity and colon cancer

| Study                     | Study Type                                   | Key Findings                                                                                                                                                                                                                                                                                                                                                        | References |
|---------------------------|----------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Giovannucci et al. (1996) | Cohort Study                                 | Increased physical activity is linked to a significantly lower risk of colon cancer, particularly in men                                                                                                                                                                                                                                                            | [139]      |
| Wolin et al. (2009)       | Meta-analysis                                | Both moderate and vigorous physical activity lowers colon cancer risk.                                                                                                                                                                                                                                                                                              | [140]      |
| Meyerhardt et al. (2009)  | Cohort Study                                 | In a large cohort of men with history of non-metastatic colorectal cancer, greater physical activity was associated with lower risk of colorectal cancer-specific and overall mortality                                                                                                                                                                             | [141]      |
| Kuiper et al. (2012)      | Prospective cohort study                     | Recreational physical activity before and after colorectal cancer diagnosis, but not BMI, is associated with more favorable survival                                                                                                                                                                                                                                | [142]      |
| Boyle et al. (2013)       | Cohort Study                                 | Physical activity, BMI and smoking may influence survival after a diagnosis of colorectal cancer, with more pronounced results found for females than for males                                                                                                                                                                                                     | [143]      |
| Moore et al. (2016)       | Prospective Cohort                           | High levels of leisure-time physical activity reduce colon cancer risk by 16%                                                                                                                                                                                                                                                                                       | [133]      |
| Mahmood et al. (2017)     | Systematic Review and Meta-Analysis          | Evaluated domain-specific physical activity (occupational, transport, household, and recreational) in relation to colorectal cancer risk. Found that recreational physical activity was associated with a significant reduction in colorectal cancer risk, while occupational, transport, and household activities did not show a statistically significant effect. | [144]      |
| Kim et al. (2019)         | Randomized Controlled Trial                  | Investigated the effects of a 12-week home-based exercise program on quality of life and physical activity levels in colorectal cancer survivors. The program led to significant improvements in quality of life and increased physical activity levels among participants.                                                                                         | [145]      |
| Choy et al. (2022)        | Systematic Review and Meta-Analysis          | Exercise was associated with increased overall survival in colorectal cancer patient's post-resection, supporting the promotion of exercise interventions.                                                                                                                                                                                                          | [146]      |
| Brown et al. (2023)       | Observational Study                          | Postoperative physical activity in stage III colon cancer patients was associated with improved disease-free survival, particularly within the first-year post-treatment.                                                                                                                                                                                           | [147]      |
| Diao et al. (2023)        | Systematic review and dose-response analysis | This study demonstrated a significant inverse relationship between total physical activity and the risk of breast, gastric, liver, colon, and lung cancers                                                                                                                                                                                                          | [148]      |
| Himbert et al. (2023)     | Prospective, multicenter ColoCare Study      | Physical activity and BMI were individually associated with disease-free survival among colorectal cancer patients. Physical activity seems to improve survival outcomes in patients regardless of their BMI                                                                                                                                                        | [149]      |
| Stein et al. (2024)       | Cohort Study                                 | A pattern of early- plus late-day activity is related to reduced colorectal cancer risk, beyond the benefits of overall activity.                                                                                                                                                                                                                                   | [150]      |
| Smit et al. (2024)        | Cohort Study                                 | Female sex and higher fatigue scores were consistent determinants of lower moderate-to-vigorous PA during sport and leisure time (MVPA-SL) levels among all CRC patients, and MVPA-SL levels were lowest at 6 months postdiagnosis                                                                                                                                  | [151]      |
| Zou et al. (2025)         | Cohort Study                                 | Low physical activity increases the risk of colon cancer, while moderate to high-intensity physical activity can reduce the risk of colon cancer                                                                                                                                                                                                                    | [152]      |

### Effect of exercise on insulin-like growth factor 1 (IGF-1) signaling pathway and CRC

Exercise profoundly impacts the molecular mechanisms influencing cancer development, particularly through its effects on the insulin-like growth factor 1 (IGF-1) signaling pathway. IGF-1 is a peptide hormone that plays a central role in regulating cell growth, survival, and proliferation. Normally, IGF-1 binds to its receptor, the IGF-1 receptor (IGF-1R), on cell surfaces. This activation triggers intracellular signaling cascades, notably the PI3K/Akt and Ras/MAPK pathways, which drive cellular processes like growth, survival, and division. These pathways are tightly regulated in healthy cells; however, overactivity can lead to uncontrolled cell proliferation and resistance to apoptosis, the process that typically removes damaged or abnormal cells [3, 62–64]. In CRC, elevated IGF-1 levels contribute to cancerous growth by promoting unchecked colonic cell division. High IGF-1 levels can activate the aforementioned signaling pathways, creating an environment where cells are more resistant to programmed cell death and more prone to proliferating in an uncontrolled manner. This gives rise to the formation of tumors and can enhance their survival, allowing cancer cells to persist and grow without the usual regulatory checks [65, 66]. However, exercise modulates IGF-1 levels. Regular physical activity reduces circulating IGF-1 concentrations. By decreasing IGF-1 levels, exercise indirectly dampens the activation of signaling pathways that stimulate excessive cell division and survival. The reduced levels of IGF-1 lead to less activation of the IGF-1R and its downstream signaling cascades. As a result, the cellular processes driven by these pathways—such as proliferation and resistance to cell death—are significantly attenuated, making it less likely that cells will undergo malignant transformations [54, 63, 67, 68]. Moreover, exercise enhances the body's DNA repair capacity. Physical activity increases DNA repair mechanisms, reducing the likelihood of cancer-causing mutations. It also promotes apoptosis, ensuring damaged or abnormal cells are efficiently removed. For example, exercise enhances the expression of tumor suppressor genes like p53, which triggers apoptosis in response to DNA damage or cellular stress [69, 70]. Together, these mechanisms create a protective environment that reduces the risk of cancer formation. By decreasing IGF-1 levels and interfering with the associated growth-promoting pathways, exercise disrupts the signaling networks that would normally allow cancer cells to thrive. Additionally, by boosting DNA repair and promoting the elimination of abnormal cells through apoptosis, exercise helps to safeguard against the accumulation of genetic mutations that could ultimately lead to cancer. This combination of molecular effects emphasizes the important role that physical activity plays in cancer prevention and overall cellular health [71–73].

Beyond direct molecular effects, regular exercise also aids general metabolic health, weight management, and immune function, further reducing cancer risk. The benefits of physical activity, therefore, go beyond just the mechanical effects on inflammation and signaling pathways. Exercise helps create an overall healthy internal environment that is less conducive to the development of cancer, particularly in the colon. By improving systemic functions like metabolism, immune response, and cell regulation, exercise provides a multi-faceted approach to cancer prevention. This explains why physical activity is a key strategy for reducing CRC risk and supporting recovery in diagnosed individuals (Fig. 1) [20, 74].

### Effect of exercise on leptin and Ghrelin and CRC

Leptin and ghrelin are key hormones regulating energy balance, appetite, and metabolism. Leptin, secreted primarily by adipose tissue, functions as a satiety hormone, signaling the brain that energy stores are sufficient and suppressing appetite. Ghrelin, mainly produced by the stomach, stimulates hunger and promotes food intake by acting on the hypothalamus. These hormones are crucial in maintaining body weight and energy homeostasis [3, 75]. Exercise influences leptin and ghrelin levels, contributing to metabolic regulation. Physical activity generally increases ghrelin and reduces leptin. The decrease in leptin is likely due to reduced fat mass from exercise, while increased ghrelin may be a compensatory mechanism to balance energy expenditure by promoting hunger. However, the exact response varies depending on exercise intensity, duration, and individual metabolic state [3, 76].

The relationship between these hormones and CRC is of interest because obesity and metabolic dysregulation are major risk factors for CRC development and progression. Studies suggest that exposing CRC cells to adipocytes (fat cells) and pre-adipocytes (immature fat cells) can enhance tumor cell proliferation, potentially due to altered secretion of metabolic hormones like leptin and ghrelin. Leptin, elevated in obesity, is associated with increased cancer cell growth, angiogenesis (new blood vessel formation), and resistance to apoptosis (programmed cell death), all of which contribute to tumor progression. Conversely, ghrelin has a more complex role, with some studies suggesting potential protective effects against tumor growth [3, 77]. In a study by Nuri et al., 30 men with CRC participated in an 8-week walking program, with three 45-minute sessions per week at 50–60% of their target heart rate. The results showed a significant increase in ghrelin levels, but no changes in plasma leptin levels or insulin resistance. This suggests that moderate-intensity exercise may regulate hunger-related hormones but not significantly alter leptin levels in the short term [78]. In another study by Piringer et al., CRC patients

engaged in a year-long exercise regimen three times per week, leading to increased adiponectin and leptin levels. Adiponectin is an anti-inflammatory hormone with beneficial metabolic effects, including improved insulin sensitivity and tumor growth inhibition. The increased leptin in this study contrasts with the previous study, suggesting that exercise duration and intensity influence hormonal responses differently [79]. Overall, these findings highlight that exercise modulates metabolic hormones in CRC patients, potentially influencing tumor progression and metabolic health. While the exact mechanisms are under investigation, these hormonal changes suggest that regular physical activity may improve metabolic balance and mitigate CRC progression (Fig. 1) [3].

#### Effect of exercise on oxidative stress and CRC

Regular physical activity combats oxidative stress, a significant factor in cancer initiation and progression, including CRC. Oxidative stress occurs due to an imbalance between reactive oxygen species (ROS) production and the body's antioxidant defense systems. Excessive ROS can damage cellular components such as DNA, proteins, and lipids, leading to mutations and promoting cancer development [80–82]. Exercise enhances the body's antioxidant defenses, increasing antioxidant enzyme production, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase. These enzymes help neutralize ROS, reducing oxidative damage and potentially lowering CRC risk. Additionally, physical activity stimulates mitochondrial function and improves cellular repair, further protecting against oxidative stress-related DNA mutations that may lead to cancer [3, 81].

Exercise counteracts oxidative stress, making it a potential CRC therapeutic approach. Perse et al. found that while exercise protects by reducing oxidative stress, a high-fat mixed lipid (HFML) diet significantly weakens this benefit. In their study, HFML consumption reduced exercise's protective impact on colon carcinogenesis in rats and influenced oxidative markers in the large bowel and serum enzyme levels (Fig. 1) [83]. Additionally, endurance swimming was shown to prevent lipid peroxidation in the soleus muscle of HFML-fed rats by increasing antioxidant enzyme activity. However, despite exercise's benefits, DMH-induced colon carcinoma impaired antioxidant function in the heart tissue, suggesting that exercise alone is not always enough to counteract cancer-related oxidative stress in all organs. Therefore, exercise enhances antioxidant capacity and protects against CRC, but its effectiveness can be diminished by a high-fat diet or severe oxidative damage in certain tissues [3, 82].

#### Effect of exercise on apoptosis and CRC

Apoptotic pathway dysfunction, essential for tissue balance, is a key factor in tumor development. However, limited research exists on the effects of exercise on apoptosis in CRC [84]. Darband et al. found that an 8-week moderate-intensity exercise program reduced ACF and improved colon architecture in DMH-induced CRC rats. Exercise also increased apoptosis, as indicated by a higher Bax/Bcl-2 ratio and elevated caspase-3 activation [85]. Similarly, another study on ApcMin/+ mice showed that moderate-intensity exercise reduced colon polyp formation by 35% and altered Bax expression in colon tissue. These findings suggest exercise plays a key role in regulating apoptosis; further research is needed to understand its full impact on CRC [86].

#### The role of epigenetics in CRC

Epigenetics studies heritable and stable changes in gene expression that occur through alterations in the chromosome rather than the DNA sequence. Key epigenetic processes, including DNA methylation, histone modifications, and non-coding RNA actions, are implicated in CRC development and progression. These mechanisms are critical in tumorigenesis by influencing gene expression, particularly genes involved in cell growth and differentiation (Table 2).

#### DNA methylation

DNA methylation is crucial in gene regulation in CRC, influencing gene expression via modifications at CpG sites. Hypermethylation silences tumor suppressor genes, contributing to cancer progression. ADHFE1, CNN1, NR3C1, SFRP, ITGA4, and ADAMTS14 are among the genes identified as hypermethylated in CRC, affecting processes like cell cycle regulation, angiogenesis, and prognosis. ITGA4 hypermethylation is a potential biomarker for early CRC detection, while high ADAMTS14 expression is associated with poor patient outcomes (Fig. 2) [87, 88]. Conversely, hypomethylation plays a role in tumorigenesis by activating oncogenes like CMYC and HRAS, leading to genomic instability. Folate intake influences the impact of MTHFR polymorphisms (C677T, A1298C) on CRC risk, with DNA methylation levels varying according to folate metabolism. HER3 hypomethylation is linked to CRC development, suggesting its potential as a diagnostic biomarker [88, 89]. LINE-1 and L1-MET hypomethylation in colorectal adenomas is associated with increased CRC risk [90]. KRAS mutations, occurring in 30–40% of CRC cases, drive uncontrolled cell proliferation and confer resistance to anti-EGFR therapy. SLC25A22 contributes to increased DNA methylation by promoting succinic acid accumulation, activating the Wnt/ $\beta$ -catenin pathway, leading to tumor growth and treatment resistance. These findings

**Table 2** Important studies related to the role of epigenetic changes in colon cancer

| Study                  | Epigenetic Alteration                                                                | Key Findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | References |
|------------------------|--------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Schuebel et al. (2007) | Hyper-methylation of DNA in genes like IRAK3, CDO1, ADAM2, and SYCP3                 | Hyper-methylation of DNA in genes such as IRAK3, CDO1, ADAM2, and SYCP3 is crucial for the survival and proliferation of cancer cells, whereas demethylation of these genes induces cell death and apoptosis.                                                                                                                                                                                                                                                                                                                                                                                                                           | [153]      |
| Vogel et al. (2009)    | Hypermethylation in promoter of DNA repair genes such as MLH1 and MGMT               | MLH1-hypermethylated cancers exhibit a reduced frequency of APC and KRAS mutations while displaying an increased incidence of BRAF mutations, indicating their unique development from an MGMT methylator route.                                                                                                                                                                                                                                                                                                                                                                                                                        | [154]      |
| Chen et al. (2009)     | downregulation of miR-143                                                            | The downregulation of miR-143 stimulates the RAS-RAF-MEK pathway, which targets the mRNA translation of the oncogene KRAS and inhibits colorectal cancer progression.                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | [155]      |
| Nakazawa et al. (2011) | dysregulation of H3K9me2 levels                                                      | The widespread dysregulation of H3K9me2 levels is a significant epigenetic occurrence in the progression and carcinogenesis of colorectal cancers.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | [156]      |
| Peng et al. (2013)     | Aberrant methylation of the PTCH1 gene promoter                                      | It indicates that abnormal methylation of the PTCH1 promoter may serve as an early starting factor in colon carcinogenesis.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | [157]      |
| Benard et al. (2014)   | Hypermethylation in promoter of apoptosis-related genes such as Apaf1, Bcl2, and p53 | The methylation of the intrinsic apoptotic pathway genes Apaf1, Bcl2, and p53 links with the tumor's apoptotic state.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | [158]      |
| Liang et al. (2017)    | APC promoter hypermethylation                                                        | APC promoter hypermethylation is significantly associated with CRC risk                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | [159]      |
| Han et al. (2017)      | overexpression of miR-429                                                            | miR-429 facilitates the growth and metastasis of CRC by directly targeting HOXA5.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | [160]      |
| Shen et al. (2020)     | N6-methyladenosine (m6A) modification                                                | m <sup>6</sup> A modification accelerates CRC progression by facilitating the glycolytic process of cancer cells                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | [161]      |
| Chen et al. (2020)     | m <sup>6</sup> A modification                                                        | METTL14 inhibits CRC growth and metastasis by downregulating lncRNA XIST                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | [162]      |
| Hu et al. (2020)       | loss of HDAC2 expression                                                             | The reduction of HDAC2 expression facilitates the EMT-driven lung metastasis of CRC via the lncRNA H19/miR-22-3P/MMP14 pathway.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | [163]      |
| Jiang et al. (2021)    | LINE-1 Hypomethylation                                                               | The research indicated that LINE-1 methylation diminished in correlation with indicators of more advanced neoplasia, such as size and extent of dysplasia.                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | [164]      |
| Zhang et al. (2022)    | high expression levels of LINC01094, H19, and MALAT1                                 | Elevated expression levels of LINC01094, H19, and MALAT1 are strongly correlated with metastasis and unfavorable prognosis in colorectal cancer patients.                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | [165]      |
| Alvandi et al. (2022)  | Decrease SCFAs                                                                       | 70.4% of high-risk CRC people demonstrated markedly reduced levels of acetate, propionate, butyrate, or total short-chain fatty acids.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | [166]      |
| Jiang et al. (2024)    | Methylation in protein-coding genes TMBIM1/PNKD, CXCR5 and TMEM110                   | Methylation may partially mediate the harmful effects of air pollution on colorectal cancer, with reference to epigenetic modifications in the protein-coding genes TMBIM1/PNKD, CXCR5, and TMEM110.                                                                                                                                                                                                                                                                                                                                                                                                                                    | [167]      |
| Bian et al. (2024)     | Downregulation of LINC01852                                                          | LINC01852 is crucial in inhibiting CRC malignancy and chemoresistance through the regulation of SRSF5-mediated alternative splicing of PKM.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | [168]      |
| Xu et al. (2025)       | FOXN3 overexpression                                                                 | FOXN3 overexpression suppresses CRC cell proliferation, motility, invasion, stemness, and tumorigenesis via deactivating the Wnt/ $\beta$ -catenin signaling pathway.                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | [169]      |
| Wu et al. (2025)       | Epigenetic Suppression of miR-137                                                    | miR-137 enhances the degradation of c-Myc and $\beta$ -catenin through the inhibition of RNF4, thereby affecting protein stability and the inhibition of the Wnt pathway. miR-137 undergoes epigenetic silencing via DNA methylation and trimethylation of H3K27 mediated by EZH2. This process regulates the Wnt signaling pathway through the targeting of RNF4, resulting in the destabilization of c-Myc and $\beta$ -catenin. The restoration of miR-137 or the inhibition of RNF4 significantly reduces CRC cell proliferation, migration, invasion, and tumor growth, underscoring its potential as a therapeutic target in CRC. | [170]      |

highlight the critical role of DNA methylation alterations in CRC progression and provide potential diagnostic and therapeutic targets [88, 91, 92].

**Histone modifications**

Histone modifications are crucial in CRC, influencing gene expression through acetylation, methylation, and phosphorylation. These modifications regulate oncogene overexpression and tumor suppressor gene inactivation, contributing to CRC development. Histone acetylation,

controlled by histone acetyltransferases (HATs) and histone deacetylases (HDACs), affects chromatin structure and gene transcription. Excessive HDAC activity disrupts this balance, leading to CRC progression. HDAC inhibitors, such as gossypol and HIPK2, have shown promise in reducing CRC cell growth by promoting histone hyperacetylation. Additionally, dietary components, particularly short-chain fatty acids like butyrate produced by gut bacteria, can influence histone acetylation and suppress CRC progression (Fig. 2) [88, 93–95]. Exercise

## DNA Methylation

### Hypermethylation (●):

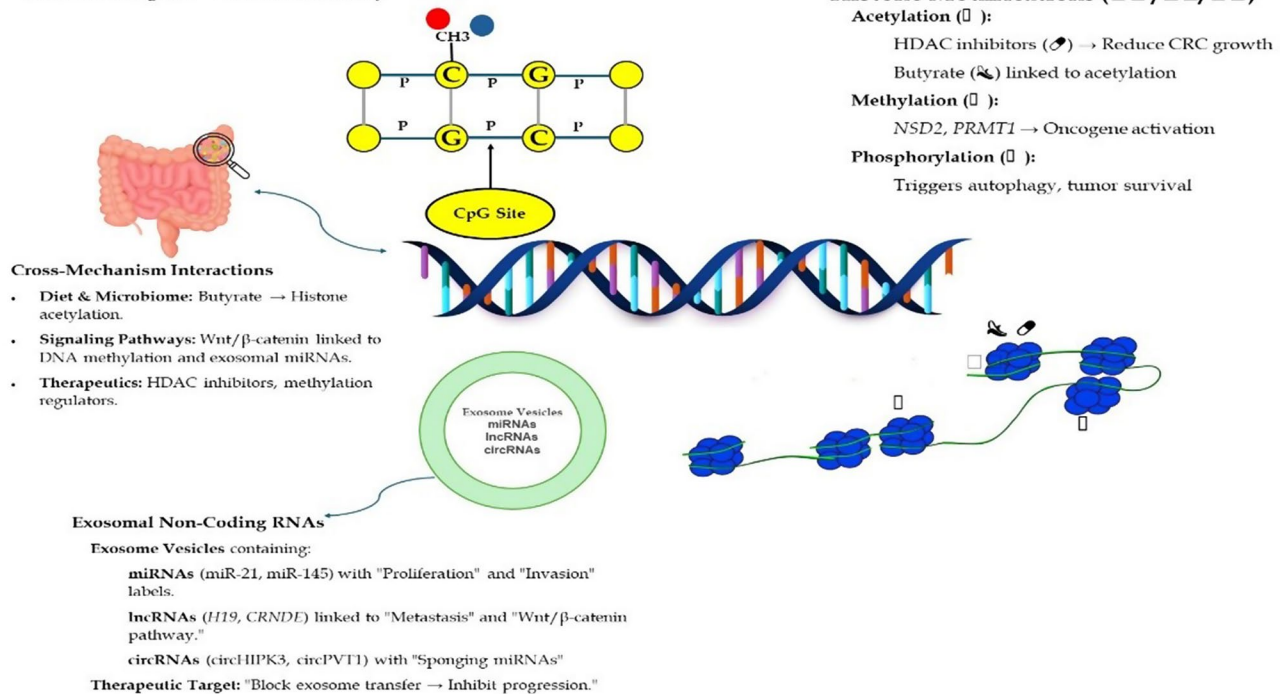
Silenced tumor suppressor genes (*ADHFE1*, *CNN1*, *SFRP*)

Silences tumor suppressors → Cancer progression

### Hypomethylation (●):

Activated oncogenes (*CMYC*, *HRA5*)

Activates oncogenes → Genomic instability



**Fig. 2** The role of epigenetics on CRC progression

correlates with the acetylation of various lysine residues in human skeletal muscle histones, leading to chromatin decompaction and the activation of transcription for specific exercise-responsive genes. Intense strength exercise enhances histone H3 acetylation [9, 96]. Histone methylation, regulated by methyltransferases and demethylases, plays a dual role in CRC. Abnormal methylation can activate oncogenes and promote malignant transformation. Increased expression of histone demethylases in CRC tissues enhances cancer cell proliferation and invasion. Genes like atypical chemokine receptor 3, abhydrolase domain-containing 5, and *NSD2* have been identified as key players in histone methylation-related carcinogenesis. *PRMT1*, for example, promotes CRC progression through asymmetric demethylation, while low levels of lysine demethylase 6 A are linked to poor prognosis due to increased methylation [95, 97, 98]. A majority of the studies reviewed indicated that exercise interventions can lead to notable alterations in DNA methylation. Studies assessing particular CpG sites noted heightened methylation associated with *RANKL*, *FKBP5*, *AURKA*, *BPIFA*, *BRCA1*, *p66Shc*, and *ASC* genes. Concerning global methylation, investigations have indicated a notable downregulation as a consequence of exercise.

In a similar vein, analyses of the epigenome have shown that exercise modifies the DNA methylation profile. Most trials align with earlier cross-sectional studies that indicate notable effects of exercise on DNA methylation [99, 100]. Histone phosphorylation is another key regulatory mechanism in CRC, influencing gene transcription and cancer progression. Dysregulated phosphorylation of histones H2B and H4, mediated by enzymes like *EZH2* and anti-silencing factor 1, activates autophagy-related genes, aiding tumor survival. Certain compounds, such as 2-[[3-(2,3-dichlorophenoxy) propyl] amino] ethanol hydrochloride, can induce DNA damage and apoptosis in CRC cells through phosphorylation-mediated signaling pathways. Additionally, the kinase *VprBP*, which is over-expressed in CRC, promotes tumor growth by regulating histone H2A phosphorylation [95, 101–103].

Phosphorylation takes place at the serine and tyrosine residues of histones. Engaging in physical activity leads to elevated levels of H3 serine phosphorylation within skeletal muscle tissue. Consequently, specific signaling pathways such as *AMPK*, *MAPK*, *PKA*, *PKC*, and *CaMK-II* play a crucial role in phosphorylation-dependent signaling in skeletal muscle during exercise [9, 104]. The existing theory indicates that H3 phosphorylation is a

prerequisite for acetylation, implying a sequential regulation of chromatin decompaction and the mechanisms required for transcription initiation [105]. Overall, histone modifications are key epigenetic mechanisms that drive CRC progression. Understanding these modifications offers potential therapeutic targets, with HDAC inhibitors, methylation regulators, and phosphorylation-targeting agents emerging as promising treatment strategies. Additionally, dietary and microbial influences on histone modification pathways present new opportunities for CRC prevention and management [95].

### Exosomal non-coding RNAs

Exosomes are small extracellular vesicles that play a significant role in the intercellular exchange of non-coding RNAs (ncRNAs), impacting various biological processes, including cancer progression. In CRC, exosomes mediate the transfer of ncRNAs, such as microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), contributing to tumor growth, metastasis, and drug resistance. These ncRNAs influence CRC pathogenesis by regulating gene expression, cellular behavior, and signaling pathways, making exosomes a potential source for early disease detection and monitoring (Fig. 2) [106, 107]. miRNAs are the most studied exosomal ncRNAs in CRC. Specific miRNAs, including miR-21, miR-29a, miR-92a, miR-143, and miR-145, are dysregulated in CRC exosomes, playing crucial roles in cell proliferation, apoptosis, migration, and invasion. For instance, miR-21 promotes CRC cell proliferation and invasion by targeting tumor suppressor genes, whereas miR-145 inhibits cell migration and invasion by targeting oncogenes. Exosomal miRNAs also regulate key signaling pathways, such as the Wnt/ $\beta$ -catenin and PI3K/Akt/mTOR pathways, involved in CRC progression. Additionally, exosomes transfer miRNAs between cancer cells, facilitating cancer progression and drug resistance. For example, exosomal miR-21 transfer from CRC cells to fibroblasts activates cancer-associated fibroblasts, enhancing cell migration and invasion [108–111]. Exosomal lncRNAs are also involved in CRC pathogenesis. lncRNAs, such as H19 and CRNDE, are upregulated in CRC exosomes, contributing to cell expansion, invasion, and metastasis by modulating pathways like Wnt/ $\beta$ -catenin and regulating key genes. Exosomal lncRNAs are proposed as potential diagnostic and prognostic markers, and targeting them may disrupt the tumor microenvironment, potentially inhibiting CRC progression. Long non-coding RNA colon cancer-associated transcript 1 (CCAT 1) is overexpressed in CRC and is associated with CRC tumorigenesis and treatment outcome [107, 112–114]. Circular RNAs (circRNAs) in exosomes are emerging as CRC regulators. For example, circHIPK3 is downregulated in CRC exosomes, suppressing cell proliferation

and invasion by sponging miR-7, whereas circPVT1 and circMYH9 are upregulated, promoting CRC cell proliferation and migration by sponging miRNAs like miR-30c and miR-194-3p, respectively. Targeting exosomal circRNAs could offer new therapeutic approaches to inhibit CRC progression and metastasis [107, 110, 115]. In summary, exosomal ncRNAs play a pivotal role in CRC development and progression, serving as potential biomarkers and therapeutic targets. Modulating the intercellular exchange of ncRNAs through exosomes could offer new strategies for early CRC detection, prognosis, and treatment (Fig. 1) [107].

### Relationship between exercise and epigenetics

#### *Impact of exercise on gene expression and CRC*

Exercise enhances the body's natural defense against CRC by boosting immune cell activity, increasing tumor immune infiltration, and upregulating genes for immune surveillance. It strengthens natural killer (NK) cells, which detect and eliminate cancer cells, by improving their circulation, cytotoxicity, and tumor infiltration. This effect is mediated by increased interferon-gamma (IFN- $\gamma$ ), enhancing NK cell function and immune cell recruitment [116]. Exercise also activates cytotoxic T lymphocytes (CD8+ T cells), which recognize and destroy cancer cells by releasing apoptosis-inducing proteins like perforins and granzymes. This process is supported by dendritic cells, which improve antigen presentation and T-cell activation. Additionally, exercise shifts macrophages from the tumor-promoting M2 phenotype to the anti-tumor M1 phenotype, increasing the release of inflammatory cytokines such as TNF- $\alpha$ , IL-12, and IFN- $\gamma$ , creating a less favorable environment for cancer growth [116, 117]. Systemically, physical activity enhances immune cell circulation and tumor infiltration by increasing chemokines like CXCL9, CXCL10, and ICAM-1, hindering cancer cell evasion of immune destruction. It also upregulates genes crucial for immune surveillance, including granzyme B, perforin, IFN- $\gamma$ , and interleukin-15, strengthening NK and CD8+ T cell function. Furthermore, exercise reduces immunosuppressive factors such as regulatory T cells and myeloid-derived suppressor cells, restoring a more effective anti-tumor immune response [116, 118]. Overall, exercise creates an immune-supportive environment that suppresses tumor growth and metastasis, leading to better cancer prevention and improved outcomes for CRC patients.

#### **Exercise, micrornas, and CRC**

The relationship between physical activity and epigenetics is examined through variations in DNA methylation patterns at CpG sites within genes that play key biological roles [3, 119]. Molecular epidemiological studies have identified specific genes, including APC, MLH1,

tumor growth factor beta (TGF- $\beta$ ), cyclin-dependent kinase inhibitor p16, K-Ras (KRAS), and B-Raf (BRAF), which exhibit differential methylation between normal and cancerous colonic epithelial cells. Increased methylation of these genes is frequently observed in CRC tissues, highlighting their crucial role in CRC development and progression [3, 120]. Research exploring the connection between exercise and DNA methylation in CRC remains limited, and findings are inconsistent. Some studies, due to limitations, have not established a significant relationship between physical activity and methylation levels at the promoters of IGFBP, MLH1, BRAF, and the p15 tumor suppressor gene [3, 121, 122]. Beyond DNA methylation, the impact of exercise on miRNA expression has also been studied. Tonevitsky et al. reported that 30 min of exercise influenced the expression of miR-21, miR-27a, and miR-18a in eight adult males, all implicated in CRC development. Another study found that exercise lowered the expression of miR-342, which regulates DNMT1. Additionally, research by Kriska et al. on rats with Azoxymethane-induced CRC revealed that levels of miR-378 in the colon, muscle, and serum were inversely correlated with CRC progression. A 24-week progressive treadmill-training program (1 h per day, three times per week) not only suppressed cancer progression but also increased miR-378 expression, suggesting a potential protective effect of exercise against CRC [3, 123, 124].

### Evidence linking exercise to CRC prevention

#### *Therapeutic and molecular effects of exercise in CRC*

Table 1 indicated the relationship between physical activity and CRC. Exercise serves as both a preventive and therapeutic strategy for CRC. In CRC patients undergoing chemotherapy, physical activity improves muscle strength, cardiorespiratory fitness, emotional well-being, and sleep quality. Additionally, it supports post-treatment recovery by reducing fatigue and enhancing overall quality of life in CRC survivors [3, 52]. At the molecular level, exercise exerts protective effects through multiple mechanisms, including modulating the IGF system, reducing inflammation, promoting apoptosis, enhancing immune function, and influencing epigenetic modifications. Epigenetic changes, reversible alterations in gene expression without modifying DNA sequences, play a crucial role in cancer progression. Exercise may help restore normal epigenetic processes, contributing to anti-tumor effects and improved responses to conventional therapies [3, 125].

#### *Impact of exercise on the gut Microbiome and CRC*

The relationship between exercise and the gut microbiome has become a significant research focus, especially regarding its potential impact on CRC. Regular physical activity alters the composition and diversity of the gut

microbiome, increasing beneficial bacteria and reducing harmful pathogens. Key beneficial bacteria that thrive with exercise include *Bifidobacteria*, *Lactobacilli*, *Faecalibacterium prausnitzii*, *Akkermansia muciniphila*, *Roseburia spp.*, and *Enterococcus faecium*. These bacteria produce short-chain fatty acids (SCFAs), such as butyrate, acetate, and propionate, which protect gut health. SCFAs serve as an energy source for colon cells, regulate inflammation, and maintain gut barrier integrity, preventing harmful pathogens from entering the bloodstream. Butyrate, in particular, has anti-inflammatory properties, reducing pro-inflammatory cytokines and modulating immune cell activity in the gut, which lowers CRC risk by addressing chronic inflammation, a key contributor to cancer development [126–130]. Exercise-induced microbiome changes also influence gene expression in colon cells, with butyrate promoting epigenetic modifications like histone deacetylation. These modifications support healthy cell growth and apoptosis, reducing the likelihood of cancerous transformations. Therefore, regular exercise fosters a diverse gut microbial community, enhances SCFA production, reduces inflammation, and strengthens gut barrier function. These molecular mechanisms, including immune regulation, gut integrity, and epigenetic changes, contribute to exercise's protective role against colorectal cancer (Fig. 1) [6, 126, 129].

### Exercise during and after cancer treatment

Regular physical activity is strongly recommended for CRC prevention, with guidelines advocating for at least 150 to 300 min of moderate-intensity or 75 to 150 min of vigorous-intensity aerobic exercise per week. A combination of aerobic exercises, resistance training, and flexibility workouts maximizes health benefits [131]. Individuals should start gradually, build consistency, and address common barriers such as time constraints and motivation. For cancer patients and survivors, exercise offers significant benefits, including improved physical function, reduced fatigue, and enhanced quality of life. However, exercise programs should be tailored to individual health status and treatment regimens, with healthcare provider consultation to ensure safety and address specific needs or limitations [131, 132]. Epidemiological studies highlight a clear inverse relationship between regular exercise and cancer incidence, showing that higher physical activity levels can reduce the risk of 26 cancer types, including CRC, by 20–30%. The protective effects of exercise are attributed to multiple biological mechanisms: regulation of hormones like insulin and sex hormones, reduction of chronic inflammation, enhancement of immune function, and improvement in DNA repair processes. These mechanisms collectively create a systemic environment less favorable for cancer development and progression [131, 133]. Beyond structured exercise,

lifestyle modifications influenced by physical activity—such as weight management, improved dietary habits, better stress management, and enhanced sleep quality—also play a vital role in colorectal cancer prevention. Together, these factors underscore the importance of regular physical activity as a powerful tool for reducing cancer risk and improving overall health outcomes [3, 134].

#### ***The potential adverse effects of physical exercise on CRC***

Although physical exercise is generally beneficial for individuals with CRC, certain circumstances may lead to adverse effects. Understanding these potential risks is crucial for tailoring safe and effective exercise programs. High-intensity exercise can lead to gastrointestinal distress, especially in individuals with pre-existing digestive conditions. Intense physical exertion is associated with adverse effects such as acid reflux, gastrointestinal bleeding, and delayed gastric emptying [135]. These issues are often linked to reduced blood flow to the digestive system during vigorous activity, which may result in intestinal ischemia and dehydration. For instance, prolonged high-intensity exercise can compromise gut barrier function and increase intestinal permeability, potentially worsening symptoms in individuals with CRC [135, 136]. Individuals in vulnerable groups—such as older or frail CRC patients undergoing chemotherapy—may experience limited benefits from exercise due to pre-existing health conditions or diminished physical capacity. Research often excludes individuals with mobility impairments or serious medical conditions, despite their heightened risk of injury or fatigue during physical activity [137]. Moreover, the effects of resistance training on gastrointestinal health remain underexplored, and poorly designed programs may place additional strain on those with existing vulnerabilities [135]. The timing and intensity of exercise during the treatment process are crucial factors. While physical activity is generally associated with improved outcomes, exercising at inappropriate times—such as during the acute phases of chemotherapy—may exacerbate fatigue or hinder recovery. A recent study reported a notable 27% decline in exercise adherence among CRC patients undergoing chemotherapy, underscoring the difficulties of maintaining physical activity amid treatment-related side effects [138]. However, it is important to note that no significant adverse events were reported in supervised exercise trials [137]. A theoretical concern relates to oxidative stress. While not always explicitly addressed in studies, vigorous physical activity may elevate oxidative stress levels, which are associated with cancer progression. In contrast, moderate exercise has been shown to reduce oxidative stress and inflammation, highlighting the importance of regulating exercise intensity [3, 52]. In summary, while physical activity is generally safe and beneficial for individuals with CRC, its effectiveness can

vary based on personal health factors, treatment stages, and cancer subtypes. It is essential for patients to consult with healthcare professionals to tailor exercise programs that align with their specific conditions and phases of treatment.

#### **Conclusions**

Regular physical activity is a critical factor in reducing the risk of colorectal cancer (CRC) and improving outcomes for patients and survivors. Exercise exerts its protective effects through multiple biological mechanisms, including reducing chronic inflammation, enhancing immune function, and inducing beneficial epigenetic changes such as DNA methylation and histone modifications. It also positively influences the gut microbiome by increasing beneficial bacteria that produce anti-inflammatory short-chain fatty acids like butyrate. Additionally, exercise helps regulate hormones like insulin and IGF-1, which are linked to cancer progression, and reduces oxidative stress while improving DNA repair. Despite variations in efficacy among individuals, particularly between genders, exercise remains a powerful preventive and therapeutic tool for CRC. Tailored exercise programs can improve physical function, reduce fatigue, and enhance the quality of life for patients and survivors. By targeting inflammation, immunity, epigenetics, and gut health, exercise offers a multifaceted approach to CRC prevention and management. As research progresses, further insights into the interplay between exercise, epigenetics, and CRC will likely lead to more personalized and effective interventions, contributing to a significant reduction in CRC incidence and improved patient outcomes.

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#### **Author contributions**

Yu Sun, Ooi Boon Keat, Sogand Rajabi contributed to the study conception, design, data collection, and written manuscript. Yu Sun, Ooi Boon Keat, Sogand Rajabi read and approved the final manuscript. All authors reviewed the manuscript."

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No datasets were generated or analysed during the current study.

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#### **Ethics approval and consent to participate**

NA.

#### **Consent for publication**

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The authors declare no competing interests.

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