Am J Cancer Res 2024;14(7):3200-3221
www.ajcr.us /ISSN:2156-6976/ajcr0156888

Review Article

Role of sex steroids in colorectal cancer: pathomechanisms and medical applications

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Received March 29, 2024; Accepted June 26, 2024; Epub July 15, 2024; Published July 30, 2024

Abstract: Given that the colon represents the most extensive hormone-responsive tissue in the human body, it prompts a compelling inquiry into whether the progression of its cancer is intimately linked to hormonal dynamics. Consequently, the interplay between sex steroids - a pivotal constituent of hormones - and colorectal cancer has increasingly captivated scientific interest. Upon a comprehensive review of pertinent literature both domestically and internationally, this study delineates the present landscape of three pivotal steroids - estrogen, progestin, and androgen - in the context of colorectal cancer. More specifically, this investigation probes into the potential utility of these steroids in providing therapeutic interventions, diagnostic insights, and prognostic indicators. Furthermore, this study also delves into the mechanistic pathways through which sex steroid interventions exert influence on colorectal cancer. It was discovered that the trio of sex steroid hormones partakes in an array of biological processes, thereby influencing the onset and progression of colorectal cancer. In conclusion, this study posits that a profound interconnection exists between colorectal cancer and sex steroids, suggesting that elucidating the targets of their action mechanisms could unveil novel avenues for the diagnosis and prevention of colorectal cancer.

Keywords: Estrogens, progestins, androgens, colorectal cancer

Introduction

Colorectal cancer (CRC) has emerged as a globally prevalent malignancy, with its incidence in 2020 ranking third worldwide among all malignant tumor types. In China, CRC ranks as the second most common malignancy, with both its incidence and mortality rates being notably high on a global scale [1]. This underscores the significant global and national burden posed by CRC.

The hypothalamic-pituitary-gonadal axis, a crucial element of neuroendocrine regulation, plays a pivotal role through its influence on the testes and ovaries in secreting respective sex hormones, thereby regulating diverse physiological and pathological processes in humans. The correlation between sex hormone levels and age and gender is well established, with epidemiological studies revealing significant variances in CRC prevalence across different ages and genders [1], implying that sex hormones could be instrumental in understanding CRC pathology.

Empirical evidence suggests that early detection and preventive measures can significantly mitigate CRC mortality [2]. Currently, extensive research has been conducted on the potential role of sex hormones in modulating CRC [3], yielding insights into the mechanisms by which these hormones influence CRC pathogenesis and progression. This review aims to synthesize current research findings on the role of sex hormones in CRC, offering innovative perspectives for the diagnosis and prevention of CRC, ultimately aiming to decrease clinical CRC mortality.

Estrogens and colorectal cancer

Applications of estrogen in colorectal cancer

Within the human body, the hypothalamic-pituitary-ovarian axis serves as the principal regula-

https://doi.org/10.62347/OEBS6893

Table 1. Applications of estrogen in colorectal cancer

Sex steroid	Ways	Subject	Outcome	Reference
Estrogens	Menopausal hormone therapy (E, EP)	Perimenopausal or postmenopausal women	Reduced the risk of CRC	[5-9]
	Underuse of estrogen replacement therapy	Premenopausal women who undergo surgical menopause	Reduced the risk of CRC	[12]
	Oral contraceptives (EP)	Women of different ages	Reduced the risk of CRC	[13]
	Soy-derived phytoestrogen isoflavones	Asian populations	Reduced the risk of CRC	[14]
	Phytoestrogen sesamin	Nude mice, cells	Controlled CRC progression	[15, 16]
	Monitoring of circulating estrogen levels	Postmenopausal women	Endogenous estrogen levels were inversely associated with the risk of CRC	[20]
	Monitoring of circulating estrogen levels	Postmenopausal women	Endogenous estrogen exposure increased the risk of CRC	[21]
	Bilateral oophorectomy	Female nurses	Increased the risk of CRC	[22]
	Monitoring of circulating estrogen levels	Postmenopausal women	Endogenous estrogen levels were not associated with the risk of CRC	[23]

Notes: E: estrogen only; P: progestin only; EP: estrogen and progestin combination.

tory mechanism for estrogen production and regulation. Estrogen is secreted by the ovaries under the influence of the hypothalamus-pituitary axis. Concurrently, ovarian estrogen modulates the pituitary levels of luteinizing hormone and gonadotropin-releasing hormones through a sophisticated system of positive and negative feedback, maintaining axials homeostasis. Estradiol, the primary estrogen produced by the ovaries, stands as the most biologically potent form among all estrogens. Below we will delve into the Applications of estrogens in CRC (**Table 1**).

Exogenous estrogens

The variance in CRC development across genders has undergone thorough investigation [4]. Males exhibit a heightened susceptibility to developing CRC compared to females, with postmenopausal women experiencing a significant uptick in risk relative to their premenopausal counterparts. Consequently, the examination of hormone therapy's benefits and risks for CRC has garnered significant attention over the past two decades. In 2002, a comprehensive and authoritative randomized controlled trial elucidated the outcomes of combined estrogen and progestin hormone therapy in healthy postmenopausal women. The study simultaneously affirmed menopausal hormone therapy (MHT)'s efficacy in diminishing CRC risk and unveiled its potential to elevate the incidence of cardiovascular disease and breast cancer [5]. The deployment of MHT has sparked considerable debate due to its significant associated risks. Subsequently, international studies have been undertaken to meticulously examine the equilibrium between the advantages and perils associated with MHT usage. A nationwide cohort study in Norway revealed that MHT utilization was linked to a lower incidence of CRC, notably in its more advanced forms [6]. Furthermore, another cohort study from Sweden similarly noted that MHT is associated with a reduction in CRC risk, yet it corresponds to a marginal increase in the overall risk of cancer. Intriguingly, the heightened risk of cancer in female reproductive organs is almost counterbalanced by a decreased risk of gastrointestinal cancer [7]. A recent randomized controlled trial conducted in Korea on postmenopausal women has shown that MHT is linked to a lowered risk of both gastric cancer and CRC [8], thereby enriching MHT research with evidence from the East Asian demographics. Zhang et al. undertook a comprehensive review of prior MHT studies, and their meta-analysis of the encompassed randomized controlled trials indicated a consensus that MHT, employing a combination of estrogen and progestin, was linked to a decreased risk of CRC [9]. It is questionable whether the benefits of CRC gained by using MHT outweigh the associated risks it poses. Lobo's meta-analysis, encompassing numerous randomized controlled trials, revealed that for healthy women aged 50-60 years, the advantages of MHT significantly outweighed its risks across various age groups [10]. Research

by Manson et al. indicates that for postmenopausal women undergoing MHT, the risk of all-cause mortality, cardiovascular, and cancer-related deaths within five years is not linked to MHT usage [11]. This suggests that initiating MHT at an earlier stage in postmenopausal women may offer greater benefits. Ferris et al. developed two distinct models to evaluate the increased morbidity and mortality linked to the underutilization of estrogen replacement therapy. The cohort for both models comprised women aged 45-49 years who underwent bilateral oophorectomy and hysterectomy for benign conditions. The results demonstrated that the underutilization of estrogen therapy was linked to increased morbidity and mortality rates from coronary heart disease, stroke, and breast cancer, while cases of CRC were reduced [12]. The findings suggest that the benefits of estrogens in CRC may contradict the traditional understandings of MHT. Furthermore, the potential differential effect of the presence or absence of the ovaries and uterus on the efficacy of exogenous estrogens warrants further investigation. The global medical community acknowledges the benefits of MHT in the prevention and treatment of CRC, however, its safety as a preventive measure against CRC continues to warrant careful evaluation, which is a shortcoming of current research. The selection of the hormonal regimen, patient age, duration of treatment, and dose of treatment have been associated with variances in adverse events, highlighting potential avenues for research aimed at mitigating the therapy's negative effects.

Beyond MHT, various applications of exogenous estrogens have shown promise in diminishing the incidence of CRC. Abusal et al. provided evidence that the utilization of oral contraceptives is correlated with a decreased incidence of CRC, noting that such contraceptives, across all age groups, are associated with a lower incidence of CRC in comparison to women who have never utilized them [13]. A meta-analysis conducted by Yu et al. revealed that within Asian populations, a high dietary intake of soy-derived phytoestrogen isoflavones was linked to a lower risk of developing CRC [14]. Furthermore, sesamin, another category of phytoestrogen, have been evidenced to exhibit anti-tumor properties, effectively inhibiting the progression of colorectal cancer by curtailing the growth, metastasis, and apoptosis of tumor cells [15, 16]. The latest study offers a novel research direction. Oxindoles has previously been employed as a targeting agent for ER (+) cancer cells, while CRC cells predominantly exhibit ER (-) characteristics. Building on these findings, Bhattacharyya et al. engineered a novel structural compound, bis-arylidene oxindole, which demonstrated maximum toxicity in ER (-) CRC cell lines, thereby offering promising avenues for the development of CRC-specific anticancer drugs [17]. The studies mentioned contribute to the growing body of evidence suggesting that estrogen plays a role in mitigating CRC development, a benefit extending beyond the confines of perimenopausal and postmenopausal women to include premenopausal women, albeit with the recognition that further research in this demographic remains lacking. Moreover, estrogens derived from plants not only exhibit beneficial interventions in CRC but also harbor additional estrogenic effects, such as the alleviation of menopausal syndrome symptoms, anti-menopausal properties, and broader anticancer impacts [18, 19]. The potential of phytoestrogens as a viable alternative to traditional hormone replacement therapy poses an intriguing query, yet the empirical support from clinical experimental studies is still insufficient to substantiate this claim, indicating a clear need for further investigation. Finally, the indirect development of cancertargeting drugs by leveraging the differential expression properties of CRC sex steroids could present groundbreaking opportunities for researchers.

Endogenous estrogens

In contrast to the aforementioned research on exogenous estrogens, a consensus has yet to be reached regarding the role of endogenous estrogens. A case-control investigation endeavored to elucidate the relationship between endogenous estrogen and the risk of CRC, focusing on circulating estrogen levels in postmenopausal women, and revealed a negative correlation between circulating estrogen levels and CRC risk [20]. Conversely, findings from an additional cohort study presented divergent conclusions, indicating that exposure to endogenous estrogens heightens the risk of CRC in postmenopausal women, especially when reproductive history serves as a surrogate for

lifetime estrogen exposure [21]. A randomized controlled trial identified an association between ovariectomy and an elevated incidence of CRC, notably reporting the highest incidence among women who underwent bilateral ovariectomy [22]. Oophorectomy results in diminished levels of endogenous circulating estrogens, with this investigation may offering evidence for a negative association between endogenous estrogen levels and CRC risk. Conversely, an alternative meta-analysis intimates conflicting findings, with its aggregated results failing to establish a correlation between endogenous circulating estrogen levels and CRC risk in postmenopausal women [23]. The divergent outcomes of these studies have catalyzed a reconsideration of the ovary's role in mediating the relationship between estrogen and CRC. A randomized trial elucidated that the decision to undergo or forego tubal oophorectomy did not impact CRC outcomes in postmenopausal women subjected to treatment with exogenous estrogens [24]. These observations indicate that current research into the association between endogenous estrogens and CRC development is mired in controversy. The essence of these disputes likely hinges on the selection of indicators for gauging endogenous estrogen levels, the role of the ovary - the principal site of endogenous estrogen production - and the seemingly marginal involvement of the ovary in the action of exogenous estrogens on CRC progression. Therefore, focusing on the quantification of ovarian and circulating estrogen levels may become a pivotal question to address in future research.

Gender dimorphism

In recent times, an extensive array of research has been devoted to exploring the potential protective role of estrogen against CRC in women, yet the analogous anti-tumor efficacy in men remains underexplored. The clinical application of estrogen in males as an intervention in the CRC process remains scarcely investigated, with the majority of studies being confined to animal models and in vitro experiments. Mahbub et al. demonstrated anticancer effects in CRC model mice following estrogen and progesterone intraperitoneal injections, noting alterations in sex hormone receptor levels within colon tissues. Furthermore, in a human male CRC cell line, a combined estrogen and progestin treatment regimen exhibited notable anticancer activity [25]. Milette et al. discovered that in CRC mice, hepatic metastases diminished concomitantly with reductions in estrogen levels, a phenomenon exclusively observed in female mice and not in their male counterparts [26]. Estrogen seems to exhibit divergent roles in the prelude to and following the onset of CRC, with this regulatory effect exhibiting sexual dimorphism. Nonetheless, the mechanisms underlying how sex differences modulate disease progression are anticipated to be multifaceted and intricate, with a current deficiency in ample evidence to comprehensively delineate them. Given the limited scope of current research, there is significant potential for further exploration of the mechanisms of estrogenic intervention in CRC, particularly considering gender differences.

Mechanisms of estrogen intervention in colorectal cancer

Given the substantial benefits of estrogens in combating CRC, a plethora of research endeavors have been dedicated to elucidating their precise mechanisms of action. At present, the consensus within the scientific community posits that estrogen's efficacy in CRC primarily operates through the mediation of estrogen receptor (ER) α and β, along with the G protein-coupled estrogen receptor (GPER) [27, 28]. Furthermore, recent discoveries have indicated that the estrogen-related receptor γ possesses the capacity to impede CRC invasion through the regulation of Wnt/β-catenin signaling, positing it as a potential tumor suppressor in CRC [29].

Below we will delve into the mechanisms of estrogen intervention in CRC (**Table 2**).

Expression characteristics of estrogen receptor α and β

In healthy colorectal tissues, both estrogen receptors ERα and ERβ are present, with ERβ being the dominant form, characterized by minimal to absent ERα expression. During the initial stages of CRC pathology, there is a marked reduction or complete absence of ERβ expression in tumor tissues, accompanied by a significant upsurge in ERα expression [30]. It is widely accepted that ERα exacerbates CRC progression through the promotion of cancer cell prolif-

Table 2. Mechanisms of estrogen intervention in colorectal cancer

Sex steroid	Factor	Way	Outcome	Reference
Estrogens	ERα	Promoted cancer cell proliferation and migration	Promoted CRC progression	[31, 32]
	ERβ	Mediation of transcription and expression of oncogenes and cancer pathways	Controlled CRC progression	[38-42]
	ERβ	Regulation of epigenetic mechanisms	Reduced the risk of CRC/ Controlled CRC progression	[43-45]
	ERβ	Regulation of cell cycle, autophagy, and apoptosis	Controlled CRC progression	[46-48]
	ERβ	Intervention of precancerous lesions	Reduced the risk of CRC	[49-51]
	ERβ	Regulation of intestinal microbiome	Controlled CRC progression	[52]
	ERβ	Modulation of the tumor microenvironment	Controlled CRC progression	[53]
	ERγ	Regulated Wnt/β-catenin signaling	Controlled CRC progression	[29]
	GPER	GPER activated by specific agonist G-1 inhibited CRC cell proliferation and induced cell cycle arrest	Controlled CRC progression	[54]
	GPER	GPER signaling interfered with relevant transcription factors to promote endoplasmic reticulum stress, resulted in growth arrest and the apoptosis of CRC cells	Controlled CRC progression	[55]
	GPER	GPER inhibited cell migration in CRC under normoxia, opposite under hypoxia	Promoted/Controlled CRC progression	[56]
	GPER	Downregulation of ASNS activates GPER1 expression	Controlled CRC progression	[57]
	GPER	Low-dose nonylphenol promoted CRC growth through GPR30-mediated activation of ERK1/2 signaling	Promoted CRC progression	[58]

eration and migration [31], with patients exhibiting high ERα levels often facing a grimmer prognosis [32]. Conversely, ERβ occupies a unique position among estrogen receptors, exerting a protective effect in CRC by hindering cancer cell proliferation and invasion while facilitating apoptosis [33]. During gene transcription, ERα and ERβ contribute to regulatory processes via both genomic and non-genomic pathways. The initiation of genomic effects involves the intricate interplay between ERα and ERβ and transcription factors such as AP1, SP1, c-Jun, and c-Fos, with each receptor playing a distinctively different role in this dynamic [34]. Estrogen's binding to ERα, facilitated by the AP1 transcription factor, triggers transcription activation. In contrast, estrogen binding to ERβ leads to a reduction of estrogen's effect in the ERα pathway [35]. Consequently, ERβ's expression in genomic actions exerts a competitive suppression on ERα's expression, effectively inhibiting the activation of downstream signaling pathways mediated by ERα (**Figure 1**). Non-genomic actions predominantly occur via the palmitoylation of ERα and ERβ, a process that anchors estrogen within the endoplasmic reticulum of the plasma membrane. It has been shown that in CRC the palmitoylation of ERα activates proliferative pathways mediated by caveolin-1, alongside ERK/MAPK and PI3K/AKT pathways that promote cell cycle progression and inhibit apoptosis [36]. Conversely, ERβ palmitoylation in CRC has an antagonistic effect, facilitating apoptosis by triggering the p38/MAPK pathway and activating caspase-3, thereby effectively counterbalancing the adverse effects prompted by ERα [37]. It appears that ERα and ERβ engage in pronounced competitive interactions within both their genomic and non-genomic mechanisms of action. Furthermore, significant attention has been directed towards the observation that ERα-mediated transcript levels diminish when ERα and ERβ are co-expressed [36], indicating that ERβ may predominantly regulate estrogen signaling. Therefore, in investigating the role of estrogen receptors in CRC intervention, our emphasis was on ERβ.

Mechanisms of estrogen receptor β intervention in colorectal cancer

Given ERβ's pivotal anti-tumor role in CRC, contemporary research posits its mechanism as

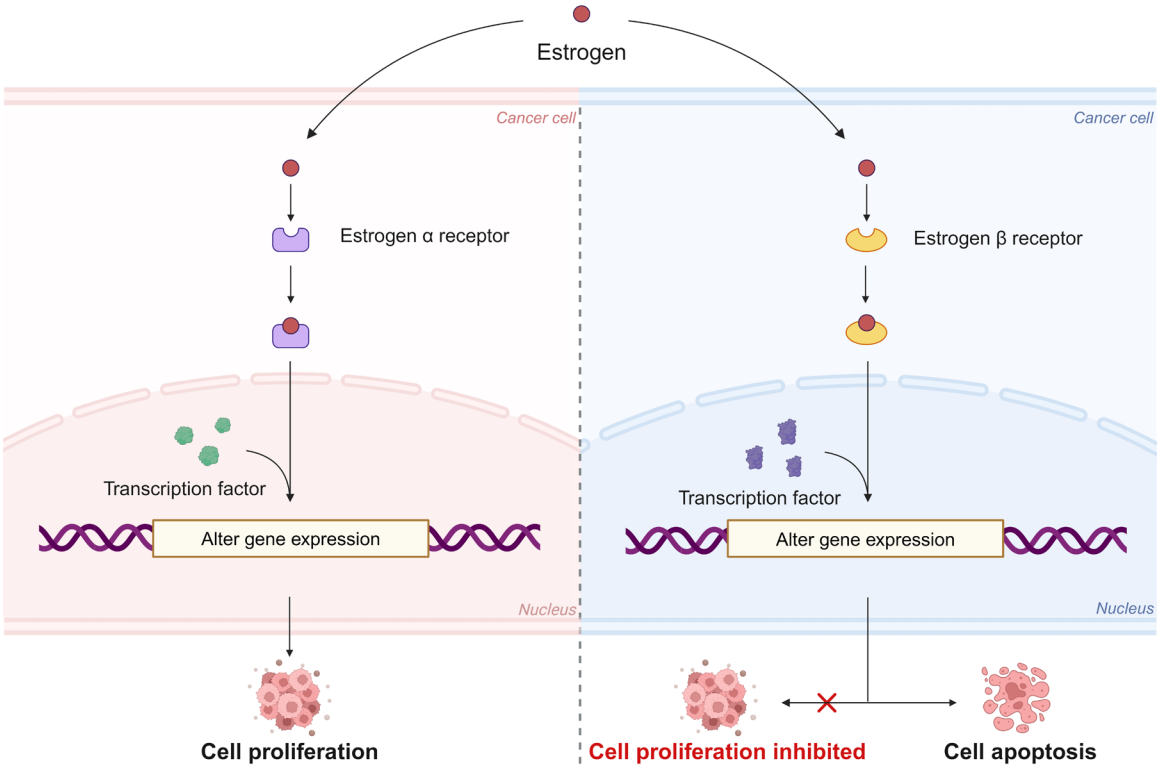

Figure 1. Mechanism of estrogen action in colorectal cancer via ERα and ERβ. ERα exacerbates CRC progression through the promotion of cancer cell proliferation and migration. Conversely, ERβ occupies a unique position among estrogen receptors, exerting a protective effect in CRC by hindering cancer cell proliferation and invasion while facilitating apoptosis. ERβ's expression in genomic actions exerts a competitive suppression on ERα's expression, effectively inhibiting the activation of downstream signaling pathways mediated by ERα.

multifaceted, involving: (1) The mediation of transcription and expression of oncogenes and cancer pathways. He et al. discovered that in CRC cells, the concentrations of estrogen and ERβ could modulate the expression of miR-135b and the mismatch repair gene MMR, suggesting estrogen's anti-tumor effects might be mediated by bolstering mismatch repair capabilities [38]. Indukuri et al. elucidated that ERβ regulates gene expression through chromatin interaction during CRC cell proliferation, migration, and apoptosis, pinpointing enrichment sites including ERE, AP-1, and TCF [39]. Liu et al. characterized WFDC3 as a tumor suppressor that disrupts TGFBR1 signaling, thereby inhibiting CRC cell migration and exerting anti-tumor effects through the modulation of ERβ-mediated transcription [40]. Zhu et al. demonstrated that calycosin targets ERβ to upregulate PTEN and suppress the expression of the PI3K/Akt signaling pathway, consequently inducing apoptosis and curbing CRC progression [41]. Nguyen et al. proposed that ERβ mediates the downregulation of PROX1 gene expression via the innovative mechanism of miR-205, thereby diminishing metastasis and proliferation of CRC cells [42]. (2) The regulation of epigenetic mechanisms. Islam et al. posited that ERβ influences the pathology of CRC through the modulation of epigenetic gene expression associated with miRNAs in CRC [43]. Neumeyer et al. uncovered a correlation between the promoter methylation of genes implicated in the pathogenesis of CRC and the expression of ERβ [44]. Ben et al. identified abundant H3K27 acetylation signals in the mRNA promoter and enhancer regions of ERβ through bioinformatics analysis. Subsequent experiments confirmed that histone deacetylase 2 enhances deacetylation by upregulating in CRC cells, thereby reducing ERβ expression and promoting CRC progression [45]. (3) The regulation of cell cycle, autophagy, and apoptosis. Hsu et al. elucidated that ERβ fosters apoptosis in CRC cells by activating p53 signaling pathways [46]. Hartman et al. proposed that ERβ governs cell cycle proteins E and D1 to halt the cell cycle, consequently mitigating

the proliferation of CRC cells [47]. Wei et al. discovered that ERβ additionally curtails CRC cell growth by inducing autophagy through CyclinD1 [48]. (4) The intervention of precancerous lesions. The transformation from inflammation to cancer constitutes a critical pathway in tumor pathogenesis. Hases et al. showed that ERβ could mitigate TNFα-induced inflammatory damage, exerting a protective influence on colitis-associated CRC [49]. However, Jang et al. presented a different perspective when they observed colitis-associated CRC model mice. They discovered that ERβ was significantly upregulated in the colonic tissues of the female group, promoting a pro-inflammatory response in early CRC by enhancing cytokine expression linked to M1 macrophage polarization in females [50]. Stevanato et al. posited that the diminished activation of ERβ accelerates CRC progression in familial adenomatous polyposis, hinting at estrogens' potential protective role through modulating CRC susceptibility [51]. (5) The regulation of intestinal microbiome. Ibrahim et al. discovered that ERβ amplifies the diversity of the intestinal flora, fostering a beneficial microbiome conducive to decelerating CRC progression [52]. (6) The modulation of the tumor microenvironment. Contemporary research has highlighted ERβ's capacity to alleviate hypoxia within the CRC tumor microenvironment, thus impeding tumor growth through the regulation of hypoxia-inducible factors [53]. Currently, the elucidation of ERβ's intervention mechanisms in CRC is becoming increasingly sophisticated, with numerous studies supporting the value of estrogen receptor intervention in CRC. Leveraging upstream and downstream regulators identified in mechanistic studies to develop precision-targeted therapeutic drugs will be at the forefront of future research.

Mechanisms of G protein coupled estrogen receptor intervention in colorectal cancer

Within the context of CRC, GPER is commonly understood to parallel ERβ in its tumor-suppressive effects via non-genomic pathways. Given the substantial overlap in mechanisms, this review briefly summarizes this section. Liu et al. discovered that GPER, when activated by the specific agonist G-1, curtails CRC cell proliferation and precipitates cell cycle arrest, underscoring the oncostatic role of GPER signaling activation in CRC [54]. Jacenik et al. highlighted that GPER signaling within CRC cells disrupts specific transcription factors, thereby inducing endoplasmic reticulum stress - a critical mechanism for initiating growth arrest and apoptosis in cancer cells [55]. Furthermore, GPER activation impedes CRC cell invasion and migration, with evidence showing that GPER curtails HT-29 and DLD-1 cell migration in CRC pathological tissues under normoxic conditions, whereas hypoxic conditions yield contrary outcomes [56]. In a recent study, Aladelokun et al. identified precise regulators of GPER. They found that the downregulation of asparagine synthetase (ASNS) activats GPER1 expression and inhibits tumor growth. The ASNS/GPER1 signaling pathway may thus emerge as a promising therapeutic target to improve the survival of CRC patients [57]. Beyond the aforementioned beneficial impacts on CRC, several studies have introduced controversy regarding this matter. Xie et al. delved into the mechanism by which the endocrine disruptor nonylphenol influences CRC, discovering that it fosters CRC growth via the GPR30-mediated activation of ERK1/2 signaling [58]. The ostensibly beneficial role of GPER signaling in CRC intimates its potential as a therapeutic target; however, apprehensions persist regarding its dual role in CRC regulation. Further research into the molecular mechanisms underlying the paradoxical effects of GPER on CRC is crucial for future investigations.

Progestins and colorectal cancer

Applications of progestin in colorectal cancer

Analogous to estrogen, progestin is produced by the ovarian corpus luteum, governed by the intricacies of the hypothalamic-pituitary-ovarian axis. It is widely accepted that progestin exerts a negative feedback regulation on the hypothalamus-pituitary axis, resulting in decreased levels of pituitary luteinizing hormone and follicle-stimulating hormone upon an increase in progesterone levels. Progesterone's principal physiological role lies in facilitating pregnancy, serving as the predominant progestin. Below we will delve into the applications of progestins in CRC (**Table 3**).

Exogenous progestins

The significance of sex hormones in CRC has been underscored by recent randomized con-

Table 3. Applications of progestins in colorectal cancer

Sex steroid	Way	Subject	Outcome	Reference
Progestins	Menopausal hormone therapy (E, EP)	Perimenopausal or postmenopausal women	Only EP rather than E reduced the risk of CRC	[59, 60]
	Menopausal hormone therapy (E, EP)	Perimenopausal or postmenopausal women	E reduced CRC specificity and all-cause mortality, EP increased specific mortality	[61]
	Oral contraceptives (EP)	Women	Reduced the risk of CRC (particularly in postmenopausal women)	[65]
	Oral contraceptives (P, EP)	Women of middle age	Reduced the risk of CRC (EP had lower risk of adverse reactions)	[66]
	Oral contraceptives (P, EP)	Women	Not associated with the risk of CRC	[67]
	Monitoring of endogenous progestin metabolic markers levels	Postmenopausal women	Endogenous progestin levels not associated with the risk of CRC	[68]
	Monitoring of progestin receptor levels	Patients with CRC who received curative resection	Progestin receptor levels not associated with survival outcomes	[32]
	Monitoring of progestin receptor levels	Human	Low levels of progestin receptor were associated with negative prognosis of CRC	[69, 70]

Notes: E: estrogen only; P: progestin only; EP: estrogen and progestin combination.

trolled trials on early MHT, incorporating two principal regimens: progestin + estrogen versus estrogen alone. While the role of estrogen has been elaborated upon, this section delves into the utility of progestin in CRC within the MHT regimen. Preliminary studies have concluded that the incidence of CRC was not mitigated by the regimen alone; a discernible effect on controlling CRC incidence was noted solely in conjunction with the combination regimen [59]. Barrett et al. deduced that a combination regimen, as opposed to monotherapy, exclusively diminish the risk of CRC; however, it increases the risk of breast cancer [60]. Moreover, the observed differences between cohorts subjected to the two regimens may hint at a distinct effect attributable to progestin. Nonetheless, given MHT's role in reducing CRC incidence, a recent study raises the question of its potential interference with survival rates in women diagnosed with CRC. Progestins seemingly exert dichotomous effects pre- and post-diagnosis, with findings indicating that the combination regimen correlates with elevated CRC-specific mortality, whereas monotherapy could potentially enhance CRC survival [61]. This controversy underscores that progestin's synergistic role with estrogen in MHT might have opposing implications before and after CRC onset, rendering progesterone not wholly classifiable as beneficial for CRC currently. Furthermore, it is yet to be elucidated whether the beneficial effects of progestins on CRC within the MHT framework arise from their inherent anticancer properties or from counteracting the detrimental effects of estrogens. Addressing this question will be an urgent task for researchers, thereby facilitating the expanded use of progestin in CRC treatment.

Oral contraceptives predominantly comprise progestins and estrogens, with the estrogenic component identified as the principal contributor to adverse events and side effects associated with their use [62]. Over time, the formulations of modern oral contraceptives have been refined to include progressively lower doses of estrogens or progestins alone, thus enhancing the safety profile of these medications [63]. Historical research has scrutinized the dual impact - both risks and benefits - of oral contraceptives on cancer incidence. Havrilesky et al. have illuminated the protective value of oral contraceptives in the primary prevention of

ovarian cancer [64]. Delving deeper into its correlations with a broader spectrum of cancers, Tsilidis et al. observed that prior utilization of oral contraceptives correlated with a modest decrement in CRC risk, a connection that was more pronounced among postmenopausal than premenopausal women [65]. Ruan et al. posited that the employment of combined oral contraceptives offers numerous advantages, notably a diminished risk of cancerous diseases like CRC, in contrast to the utilization of progestin-only pills among middle-aged women. Moreover, it mitigates the risk of adverse reactions, notably bleeding [66]. Nonetheless, recent research challenges this assertion, with findings from Michels et al. indicating that oral contraceptive usage is linked solely to a reduced risk of germline tumors, without any observed association with CRC risk [67]. The observation that oral contraceptives, primarily composed of progestins, are associated with a reduced risk of CRC development furnishes further substantiation of progestins' utility in CRC prevention. However, this area of research also harbors contentious aspects. Researchers must focus on the following issues in subsequent studies. On the one hand, this also intimates that progestins' role in CRC intervention transcends perimenopausal and postmenopausal demographics, potentially offering comparable preventive benefits in premenopausal women. Concurrently, alongside progestin-only formulations, combined contraceptives include minimal quantities of estrogen. Thus, employing oral contraceptives for CRC prevention necessitates a careful consideration of the balance between their preventive benefits and the risks posed by estrogenic components.

Endogenous progestins

The involvement of endogenous progestins in CRC intervention remains a subject of debate. Michels et al. utilized a highly sensitive assay to monitor multiple markers of progestin metabolism in postmenopausal women but did not observe a correlation with CRC risk [68]. Ye et al. examined the levels of sex hormone receptors in patients with CRC following a radical resection and find no significant association between progestin receptor expression and survival outcomes [32]. Refaat et al. delved into the expression of sex hormone receptors in CRC tissues as prognostic indicators, discovering variability in progestin receptor expression based on gender and tumor site, with overall expression linked to favorable prognostic outcomes [69]. Zhang et al. similarly reported that diminished expression of progesterone and progesterone receptors was markedly linked to an adverse prognosis in CRC [70]. Ling et al. conducted a pan-cancer analysis of progesterone and adipoQ receptor 3 (PAQR3) using bioinformatics, and found that their expression levels were lower in CRC tissues than in normal tissues. Furthermore, PAQR3 expression was negatively correlated with overall survival in CRC, indicating its diagnostic and prognostic values [71]. The utility of progestins as biomarkers for CRC diagnosis and prognosis is subject to ongoing debate, probably stemming from the insufficiency of circulating hormone level measurements to comprehensively capture their effects on tumor localization and across the human body. Consequently, there is a pressing need for the refinement and optimization of measurement protocols. Additionally, identifying the upstream regulators and downstream targets of factors with established diagnostic and prognostic values should be a primary focus of future research aimed at unlocking their therapeutic potential.

Mechanisms of progestin intervention in colorectal cancer

Folate concentrations in women exhibit a significant correlation with progestin levels, with progesterone intake via oral contraceptives resulting in diminished blood folate concentrations [72]. Extensive research has been undertaken to explore the relationship between folate and CRC, with findings regarding its role in CRC remaining a subject of debate across various studies [73]. It has been postulated that folic acid may play a pivotal role in progesterone's mechanistic intervention within the CRC paradigm. Historically, the predominant perspective posited that lower folate levels were associated with a reduced risk of CRC [74]. However, epidemiological studies have yielded conflicting outcomes, indicating a negative correlation between folate levels and CRC risk [75]. Recent investigations have demonstrated that folic acid mitigates CRC through the inhibition of proliferation and migration in the CRC cell lines COLO-205, LoVo, and HT-29 [76]. Additionally,

another study elucidated that folic acid-induced proliferation of CRC lines COLO-205, LoVo, and HT-29 was contingent on the activation of progestin receptors [77]. The aforementioned studies underpin the hypothesis that progestin might exert an indirect influence on the development and progression of CRC through the modulation of folate levels, necessitating further high-caliber evidence to substantiate this assertion.

Recognized as a pivotal endogenous progestin, Kamińska et al. discovered that while progesterone promotes the proliferation and invasiveness of the CRC cell lines DLD-1 and HT-29, it also activates traditional progesterone nuclear receptors instead of CRC cells via the activation of membrane receptor PGRMC1/NENF signaling. Furthermore, targeting the inhibition of PGRMC1 and NENF may hold therapeutic promise, with NENF's role as a secreted protein suggesting its capacity to serve as a CRC-specific circulating biomarker [78]. In contrast, Refaat et al. noted that progesterone monotherapy precipitated cell cycle arrest and apoptosis within the CRC cell lines SW480 and HT29, with these anticancer effects being negated upon the application of a nuclear progesterone receptor antagonist [69]. Zhang et al. conducted an in-depth exploration of the mechanism, revealing that progesterone elevates the expression of growth arrest and DNA damage-inducible protein α (GADD45α), subsequently inhibiting CRC cell proliferation via activation of the JNK/c-Jun pathway, resulting in cell cycle arrest and apoptosis. Drawing on the advances in CRC treatment afforded by clinical MHT, another segment of the research endeavored to elucidate the combined mechanism of action of estrogen and progesterone [70]. Drawing on the advances in CRC treatment afforded by clinical MHT, another segment of the researchers endeavored to elucidate the combined mechanism of action of estrogen and progesterone. Sasso et al. administered estradiol plus progesterone post-ovariectomy in CRC model rats, noting a reduction in cell proliferation levels, an elevation in apoptotic indices, and heightened expression of caspase-3, cleaved PARP, and cleaved caspase-8 within CRC. The elevated expression corroborated the activation of the extrinsic apoptotic pathway by the combined regimen [79]. Mahbub et al. delved into the anti-tumor potential of ovarian sex steroids, assessing their efficacy against CRC in men relative to the observed protective effects in women. Their analysis revealed that a synergistic approach involving estradiol and progesterone was more efficacious than either agent used in isolation. Moreover, through the analysis of sex hormone receptor levels, it was deduced that the combination therapy's efficacy in halting CRC progression in men could be attributed to the activation of ERβ and PGR-mediated androgen deprivation, alongside the suppression of oncogenic pathways regulated by ERα [25].

At present, unlike estrogens, research into the mechanistic action of progestin in the intervention of CRC is comparatively sparse (**Table 4**). The contentious nature of findings regarding progestin's mechanism of action has spurred speculation that endogenous estrogens could manifest divergent CRC-intervention effects via multiple mechanisms (**Figure 2**). Although evidence suggests that progestins have potential benefits for CRC, additional research is imperative to determine whether the activation of its disparate receptors can facilitate a bidirectional regulatory impact. Furthermore, distinguishing between the solitary mechanism of action of progestin and its combination with estrogen remains a challenging frontier for future research.

Androgens and colorectal cancer

Applications of androgen in colorectal cancer

Hormones originating from the hypothalamus and pituitary gland orchestrate testicular function via the hypothalamic-pituitary-testicular axis, with the produced androgens and inhibitors modulating the equilibrium of hormone secretion from both the hypothalamus and pituitary through a negative feedback mechanism. Testosterone stands as the paramount androgen in the regulation of male reproductive physiology. The applications of androgen in CRC are discussed in the following section (**Table 5**).

Given the established correlation between estrogen, progestin, and CRC, it raises the intriguing question of whether androgens, also key players in the realm of sex hormones, exhibit a similar association. In the context of androgens and oncology, Androgen Depriva-

Table 4. Mechanisms of progestins intervention in colorectal cancer

Sex steroid	Factor	Way	Outcome	Reference
Progestins	Folate	Progestins regulated folate levels, folate reduced the risk of CRC, and inhibited the proliferation and migration of CRC cells	Indirectly reduced the risk of CRC and controlled CRC progression	[72, 74, 76, 77]
	Progesterone	Activation of membrane receptor PGRMC1/NENF signal transduction promoted proliferation and the invasion of CRC cell lines DLD-1 and HT-29	Promoted CRC progression	[78]
	Progesterone	Progesterone monotherapy caused cell cycle arrest and apoptosis in CRC cell lines SW480 and HT29	Controlled CRC progression	[69]
	Progesterone	Up-regulation of GADD45α/JNK/c-Jun pathway activity blocked cell cycle and induced apoptosis to reduce CRC cell proliferation	Controlled CRC progression	[70]
	Progesterone and estradiol	Inhibited the proliferation of CRC cells and the high expression of caspase-3, cleaved PARP and cleaved caspase-8 activated the apoptosis of CRC cells	Controlled CRC progression	[79]
	Progesterone and estradiol	Promoted ERβ and PGR-mediated androgen deprivation and inhibited ERα-regulated carcinogenic pathways	Controlled CRC progression	[25]

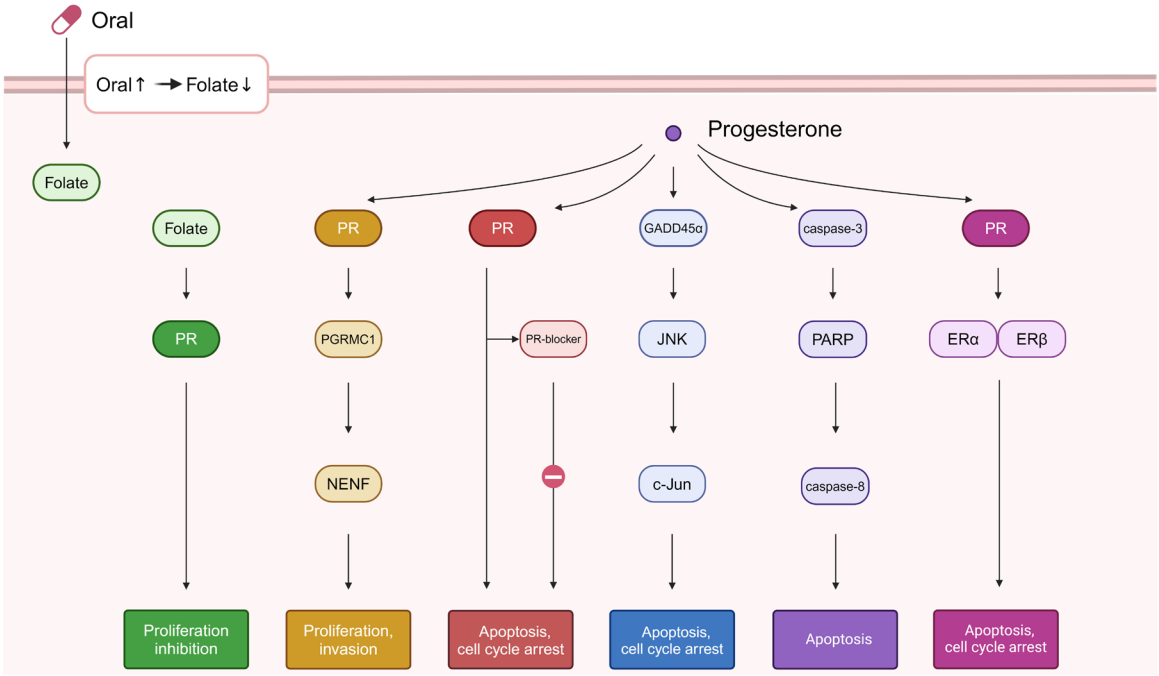

Figure 2. Functions and mechanisms of progestin regulation of colorectal cancer. Progestin may indirectly regulate CRC by regulating folate. Progestin can also directly act on CRC through various mechanisms. PR: progestin receptor.

tion Therapy (ADT) is widely acknowledged as a prevalent yet contentious treatment modality for prostate cancer. A substantial study involving a large cohort of US prostate cancer patients unveiled an intriguing phenomenon post-observation of risk events in individuals subjected to ADT, employing either gonadotropin-releasing hormone agonists or orchiectomy. Among prostate cancer patients, the employment of ADT as opposed to foregoing such treatment appears to correlate with an elevated risk of CRC, a risk that escalates with the prolonged use of ADT [80]. Supporting evidence for this phenomenon also emerges from a cohort study within the Swedish population, revealing a heightened risk of colorectal cancer in prostate cancer patients subjected to ADT relative to their unexposed, cancer-free coun-

Table 5. Applications of androgen in colorectal cancer

Sex steroid	Way	Subject	Outcome	Reference
Androgens	Androgen deprivation therapy	Patients with prostate cancer	Increased the risk of CRC	[80-83]
	Androgen deprivation therapy	Patients with prostate cancer	Not associated with the risk of CRC	[84]
	Monitoring of circulating testosterone levels	Human	Circulating testosterone levels were not associated with the risk of CRC	[85]
	Monitoring of circulating androgen levels	Men	Circulating androgen levels were not associated with the risk of CRC	[86]
	Monitoring of circulating testosterone levels	Men	Circulating testosterone levels were inversely associated with the risk of CRC	[87]
	Monitoring of circulating testosterone levels	Postmenopausal women	Circulating testosterone levels were positively associated with the risk of CRC	[88]
	Radiotherapy induced acute testicular failure	Men treated with surgical resection of the rectum	Increased risk of postoperative adverse events in CRC patients	[89]
	Monitoring of androgen receptor levels	Human	Highly expressed in CRC tissues	[69]
	Monitoring of androgen receptor levels	Patients with CRC	High expression of androgen receptor levels reduced patient survival rate	[90]
	Orchidectomy	Rats	Reduced susceptibility to colonic adenomas	[91]
	Testosterone administration	Orchiectomy in CRC male mice	Promoted CRC progression	[92]
	AR-blocker	CRC cell line	Controlled CRC progression	[69]
	Testosterone administration	CRC cell line	Promoted/controlled CRC progression	[93]

terparts, with a particular increase in the risk of adenocarcinoma in the distal colon [81]. A cohort study conducted in Spain discovered that the combined treatment of radiotherapy and ADT escalated the risk of developing secondary primary tumors, predominantly colorectal cancer [82]. A recent Canadian cohort study revealed a significant increase in the incidence of both colorectal and bladder cancers among prostate cancer patients who used ADT alone [83]. Nonetheless, there exist divergent findings that challenge the aforementioned assertions. A cohort study leveraging the UK General Practice Research Database [84] indicated that, on the whole, ADT usage did not correlate with a heightened risk of colorectal cancer development. However, an elevated risk of CRC was specifically noted in cases involving bilateral orchiectomy as a form of ADT.

In additional clinical investigations, Dimou et al. determined through a population-based observational study coupled with Mendelian randomization analysis that there exists no causal linkage between circulating testosterone levels and CRC [85]. Chan et al. in a cohort study of men, identified that diminished levels of circulating androgens were linked to an elevated risk of overall cancer and prostate cancer, yet bore no significant association with the risk of CRC [86]. Conversely, investigations conducted by other researchers have presented divergent viewpoints. Harbs et al., through a case-control study augmented by meta-analysis, uncovered a negative correlation between circulating testosterone levels and CRC risk in men, suggesting that endogenous androgens might confer a protective barrier against CRC [87]. Nevertheless, Mori et al., in a study focusing on Japanese postmenopausal women, demonstrated a positive correlation between circulating testosterone levels and the risk of CRC in this demographic [88]. Tapper et al. scrutinized male CRC patients earmarked for surgical resection and discerned that diminished preoperative testosterone levels, a consequence of radiotherapy-induced primary testicular failure, correlated with an uptick in postoperative adverse outcomes [89]. The androgen receptor (AR) plays a pivotal role in mediating androgenic functions. Refaat et al., upon examining clinical patients, unveiled that malignant colon tissues in men exhibited elevated AR protein levels relative to benign tissues, albeit without notable variations in expression based on tumor location, stage, or other variables [69]. Albasri et al. like-

wise discerned augmented AR expression within the pathological tissues of CRC patients, noting that this surge in AR expression was inversely related to patient survival rates [90]. AR appears to have potential as a prognostic marker. Regarding animal studies, Amos-Landgraf et al. discovered that male gene-deficient model rats exhibited a higher susceptibility to colorectal adenomas compared to their female counterparts. Furthermore, the incidence of colorectal adenomas diminished in rats subjected to androgen depletion via orchiectomy, highlighting androgens' potential indirect role in tumor promotion within the context of CRC's precancerous lesions [91]. Song et al. demonstrated that testosterone administration in orchiectomized mice markedly augmented the progression of azomethane/dextran sulfate sodium-induced CRC, implicating testosterone as a significant risk factor for the advancement of CRC [92]. In the realm of in vitro studies, Refaat et al. observed that treating the HT29 female CRC cell line with AR antagonists induced tumor cell apoptosis, an effect that was mitigated when the treatment was combined with testosterone [69]. Farahmandlou et al. discovered that the proliferation of HT29 cells was notably amplified upon exposure to testosterone concentrations of 10 and 100 μg/mL, while exposure to a higher testosterone concentration of 1000 μg/mL significantly curtailed cell proliferation [93].

The disparate findings across the aforementioned studies preclude a simplistic generalization of androgens as being either solely protective or conducive to CRC, underscoring the complexity of their roles. A comprehensive consideration and analysis incorporating various pathological states, gender disparities, and factors preceding and following pathogenesis are imperative to advance the study and clarify the relationship between androgens and CRC. Currently, due to the absence of clinical consensus regarding the therapeutic potential of androgens in CRC, investigations into androgen intervention have predominantly occurred within the confines of in vitro and animal studies, with clinical research primarily focusing on assessing the viability of androgens as molecular markers for the disease's diagnosis and prognosis. The potential development of future programs for androgen-based clinical control of CRC remains an open question for investigators.

Mechanisms of androgen intervention in colorectal cancer

A diverse array of sex hormone receptors is variably expressed in the colonic tissues of CRC patients, with the AR being no outlier in this pattern. The AR serves as a critical binding site for dihydrotestosterone, previously highlighted for its pivotal role in mediating androgenic actions. Catalano et al. noted the expression of both AR isoforms in normal colonic tissues; however, AR-B exhibited reduced expression in CRC tissues, whereas AR-A remained unchanged, suggesting a potential association between AR-A signaling and CRC risk [94]. Gu et al. pioneeringly revealed through animal studies that the membrane androgen receptor (mAR) is expressed in CRC tissues. They discovered that activating colonic mAR via testosterone albumin coupling elicited swift cytoskeletal reorganization and an apoptotic response, yielding anti-tumor effects in vitro [95]. Subsequent animal experiments conducted by this research group unveiled that mAR expression in CRC tissues impedes pro-survival Akt/Bad signaling, instigating an apoptotic response and obstructing CRC migration through the modulation of vinculin signaling and actin reconfiguration [96]. Yu et al. discerned that androgen-activated AR expression in mouse intestinal stromal cells curtails bone morphogenetic protein signaling, thereby fostering proliferation while stifling the differentiation of intestinal epithelial stem cells. Given that stromal cells form the ecological niche for these stem cells, this mechanism might underpin the indirect facilitation of CRC's heightened incidence in males [97]. Yang et al. observed that ARID2 germline mutations precipitate a reduction in both progression-free and overall survival rates of affected individuals, alongside diminished protein expression, deducing that AR germline mutations constitute a significant risk factor for CRC [98]. The PI3K pathway, commonly disrupted in cancer scenarios, was analyzed by Millis et al. who identified a statistically significant co-occurrence of AR and PI3K alterations in CRC [99]. This suggests that AR intervention in CRC might intricately associate with the PI3K signaling pathway. Huang et al. elucidated that extended CAG repeat sequences and the deletion of AR expression within the AR gene are linked to an elevated risk of CRC, with such alterations also correlating with diminished 5-year overall survival rates among CRC patients [100].

Contrarily, Rudolph et al. conducted a study that refuted any linkage between CAG repeats within the AR gene and the risk of CRC, finding no correlation with either overall or disease-specific survival post-CRC diagnosis [101]. The findings from a case-control study conducted by Xia et al. illuminate that methylation of the AR gene appears to play a regulatory role in CRC. An analysis of AR gene methylation patterns in peripheral blood and tissues uncovered that diminished levels of AR methylation are significantly linked to a heightened risk of CRC, a correlation that was exclusively observed in male subjects. Moreover, it was determined that there exists no significant relationship between the degree of AR methylation and the prognosis of CRC [102].

Beyond elucidating the AR mechanism's role, the implementation of ADT in prostate cancer therapy has been previously discussed. Teoh et al. identified that diminished testosterone levels in patients undergoing ADT precipitate an augmented risk of adverse outcomes, notably metabolic syndrome [103]. Metabolic syndrome, identified as a significant risk factor for CRC development [104], furnishes an explanatory framework for the heightened CRC risk observed in patients subjected to ADT, as previously outlined. Employing an azomethane/dextran sulfate sodium-induced CRC mouse model, Song et al. implemented testosterone interventions on male mice post-orchiectomy and discovered a pronounced reduction in the microbial diversity of the intestinal flora in males relative to females. They proposed that the testosterone intervention's dysregulation of intestinal flora could underpin the observed gender disparities in CRC incidence [105]. Anagnostopoulou et al. unveiled that testosterone has the capacity to counteract the anti-apoptotic influences of dehydroepiandrosterone and nerve growth factor, thereby impeding the progression of CRC through facilitating apoptosis induced by nerve growth factor receptor crosstalk within the CRC cell line [106].

Furthermore, research on androgen-related genes has established a significant link with CRC (**Figure 3**). However, the exact mechanism of intervention, potentially involving androgen action, remains undefined and present a promising avenue for future research. For instance, EAF2 has been validated for its role in modulating prostate cancer progression, with its regulation of the AR signaling pathway, alongside cell proliferation and migration, serving as a crucial mechanism in curtailing prostate carcinogenesis [107, 108]. Recently, Feng et al. discerned that overexpression of EAF2 mitigates the invasion, metastasis, and angiogenesis of CRC cells, as evidenced by pathological tissue analysis, thereby conferring anti-tumor protective effects. Furthermore, they posited that EAF2 could serve as a viable diagnostic and prognostic marker for CRC [109]. Kamata et al. deduced that the equilibrium of PARP7 within prostate cancer cells is regulated by androgen signaling, which manifests as tumor-suppressor properties [110]. Zhang et al. discovered that the upregulation of PARP7 decelerated tumor proliferation in a xenograft model of CRC, while the suppression of PARP7 elicited an inverse effect, accelerating tumor growth [111]. Liu et al. noted that PMEPA1 fosters cell proliferation in AR-positive prostate cancer cells while inhibiting growth in AR-negative counterparts, highlighting the differential impact of PMEPA1 based on AR status [112]. Zhang et al. reported that PMEPA1 initiates the TGF-β-mediated signaling pathways of bone morphogenetic proteins, thereby facilitating epithelial-to-mesenchymal transition and enhancing the proliferation and metastasis of nodal CRC [113]. Zhang et al. also discovered that PMEPA1-targeted therapy inhibits CRC growth and metastasis, while synergistically enhancing the efficacy of oxaliplatin under oxaliplatin-resistant conditions [114]. The aforementioned androgen-related factors have been demonstrated to modulate disease progression via androgenic pathways in prostate cancer. The potential of these factors to exert an intervening influence on CRC through similar androgenic mechanisms warrants further investigation.

The bulk of research investigating the mechanism of androgen intervention in CRC is focused on the AR, posited as a pivotal element in androgenic intervention within CRC. However, its mode of action is multifaceted (**Table 6**), engaging a spectrum of biological processes that necessitate comprehensive exploration in future studies. Furthermore, numerous mechanisms of androgen intervention in prostate cancer have been elucidated previously, with recent investigations revealing that certain associated factors bear relevance to CRC. This linkage presents a promising avenue for future research into the mechanisms of androgen intervention in CRC.

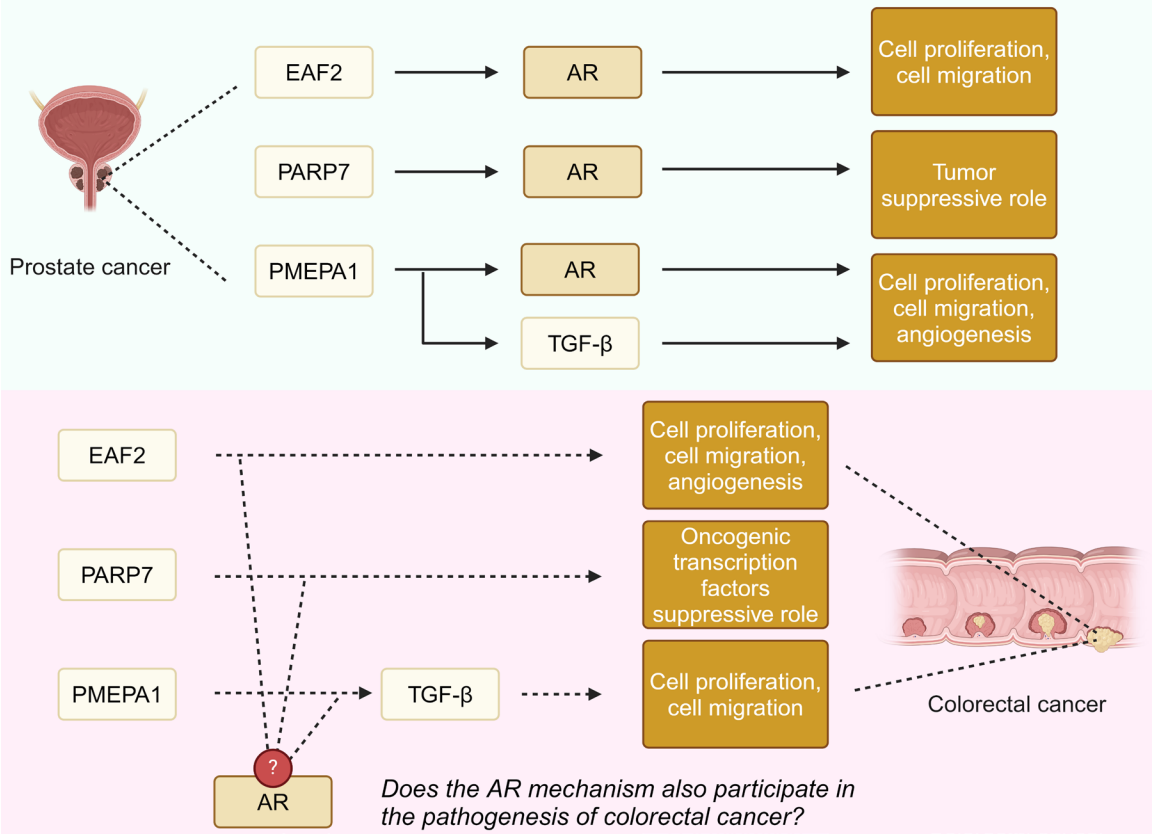

Figure 3. Potential role molecules for androgen intervention in colorectal cancer. The aforementioned androgen-related factors have been demonstrated to modulate disease progression via androgenic pathways in prostate cancer. The potential of these factors to exert an intervening influence on CRC through similar androgenic mechanisms warrants further investigation.

Conclusions and prospects

In conclusion, a substantial corpus of research evidence robustly supports the significant association between sex hormones and CRC, fostering an increasing conviction in the critical role sex hormones occupy in CRC pathogenesis. Presently, estrogen ranks as the most extensively researched among the trio of sex hormones, widely acknowledged for its favorable intervention in CRC. However, encapsulating its role within such simplistic terms does not do justice to the complexity of its mechanisms. Furthermore, estrogen leads the field in the clinical application for CRC, evidenced by a plethora of therapeutic applications and biomarker studies. The quest for pinpointing precise therapeutic targets for estrogen in CRC, contingent upon an enhanced understanding of its action mechanism, stands as a pivotal future direction to achieve augmented therapeutic gains with minimal adverse repercussions. The volume of research exploring the nexus between progestins, androgens, and CRC remains notably scant in comparison to the extensive investigations dedicated to estrogens. The utility of progestins in CRC remains equivocal, with predominant research focusing on its collaborative intervention with estrogen in clinical contexts. Independent investigations into progestin's application to CRC are comparatively rare, with a primary emphasis on biomarker-related studies. Regarding the mechanism of action, the question of whether progestin shares a similarly beneficial intervention effect with estrogen, and whether such effects are mediated solely by estrogen or through a synergistic mechanism, remains a focal point for future investigations. Androgen intervention in CRC presents a dichotomous and contentious landscape, with a pronounced dearth of research into its clinical treatment application, primarily limited to in vitro and animal studies. Nevertheless, existing studies fur-

Table 6. Mechanisms of androgen intervention in colorectal cancer

Sex steroid	Factor	Way	Outcome	Reference
Androgens	AR	Both isoforms of AR were expressed in normal colonic tissues, but AR-B expression was absent in CRC tissues and AR-A was unaffected	AR-A signaling may be associated with the risk of CRC	[94]
	AR	Activation of colonic mAR by testosterone albumin coupling induced rapid cytoskeletal reorganization and apoptotic responses in in vitro experiments, and mAR activation reduced CRC pathogenesis in animal experiments	Reduced the risk of CRC/Controlled CRC progression	[95]
	AR	Expression of mAR in CRC tissue inhibited the pro-survival signal Akt/Bad-induced apoptosis, and blocked the migration of CRC by regulating vinculin signaling and actin recombination	Controlled CRC progression	[96]
	AR	Androgen activation of AR expression on mouse intestinal stromal cells inhibited bone morphogenetic protein signaling, promoted proliferation and inhibited differentiation of intestinal epithelial stem cells	Indirectly increased the risk of CRC	[97]
	AR	ARID2 germline mutations could lead to a decrease in progression-free survival and overall survival in carriers	Promoted CRC progression	[98]
	AR	Genome analysis showed that the changes of AR and PI3K occurred together in CRC, and the intervention of AR in CRC might be through the PI3K mechanism	Promoted CRC progression	[99]
	AR	Long CAG repeated in the AR gene and the loss of AR expression were associated with an increased risk of CRC and a shorter five-year overall survival rate in patients with CRC	Increased the risk of CRC/Associated with the poor prognosis of CRC	[100]
	AR	Low level of AR methylation was significantly associated with the increased risk of CRC in men, but not with the prognosis of CRC	Increased the risk of CRC/Not associated with the prognosis of CRC	[101]
	Testosterone	After received ADT, low testosterone levels in patients could lead to metabolic syndrome	Increased the risk of CRC	[103, 104]
	Testosterone	Testosterone intervention in testicular resection CRC mice model reduced microbial diversity of their intestinal flora	Increased the risk of CRC	[105]
	Testosterone	Testosterone antagonized dehydroepiandrosterone and the scrambled nerve growth factor and induced apoptosis in CRC cell lines by crosstalking nerve growth factor receptors	Controlled CRC progression	[106]

nish evidence of its diagnostic and prognostic merits, necessitating further exploration into androgens' therapeutic potential upon elucidating their mechanism of intervention in CRC. Presently, an extensive body of research substantiates the hypothesis that CRC may exhibit sensitivity to sex hormones, underscoring the paramount importance of acquiring preventative and therapeutic targets for CRC through the meticulous investigation of sex hormones' mechanisms of action.

Acknowledgements

This study was supported by The Natural Science Foundation of Hunan Province of China (2022JJ30430, 2023JJ30452), Hunan Provincial TCM Research Program (C2023002, C2022016), Scientific Research Program of Educational Department of Hunan Province (22A0278, 21A0231), Research and Innovation Project for Graduate Students of Hunan University of Chinese Medicine (CX20230795, 2022CX06), and Aid Program for Science and Technology Innovative Research Team in Higher Educational Institutions of Hunan Province. Figure created with BioRender.

Disclosure of conflict of interest

None.

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