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REVIEW

Intricate roles of estrogen and estrogen receptors in digestive system cancers: a systematic review

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ABSTRACT Gender disparities are evident across different types of digestive system cancers, which are typically characterized by a lower incidence and mortality rate in females compared to males. This finding suggests a potential protective role of female steroid hormones, particularly estrogen, in the development of these cancers. Estrogen is a well-known sex hormone that not only regulates the reproductive system but also exerts diverse effects on non-reproductive organs mediated through interactions with estrogen receptors (ERs), including the classic (ERα and ERβ) and non-traditional ERs [G protein-coupled estrogen receptor (GPER)]. Recent advances have contributed to our comprehension of the mechanisms underlying ERs in digestive system cancers. In this comprehensive review we summarize the current understanding of the intricate roles played by estrogen and ERs in the major types of digestive system cancers, including hepatocellular, pancreatic, esophageal, gastric, and colorectal carcinoma. Furthermore, we discuss the potential molecular mechanisms underlying ERα, ERβ, and GPER effects, and propose perspectives on innovative therapies and preventive measures targeting the pathways regulated by estrogen and ERs. The roles of estrogen and ERs in digestive system cancers are complicated and depend on the cell type and tissue involved. Additionally, deciphering the intricate roles of estrogen, ERs, and the associated signaling pathways may guide the discovery of novel and tailored therapeutic and preventive strategies for digestive system cancers, eventually improving the care and clinical outcomes for the substantial number of individuals worldwide affected by these malignancies.

KEYWORDS Estrogen; estrogen receptor; cancer; digestive system cancers; gender disparity

Introduction

Gender differences in the incidence of cancer have been demonstrated in nearly all types of human cancers, including digestive system malignancies[1,2]. Of the 36 different types of cancer exhibiting a gender disparity, lung and liver cancers have been shown to be more prevalent in men than women[1]. This global trend of a higher incidence of cancer in men persists across races, even for cancers that affect both genders. Although multiple factors, such as dietary habits and risk behaviors (cigarette smoking and alcohol consumption), are believed to aid in the increased cancer risk in men, these factors alone do not fully explain the gender disparity. Even after accounting for these risk factors, males in adulthood still exhibit a greater susceptibility to cancer than females[2,3]. Following the onset of puberty, the production of sex hormones leads to the emergence of epigenetic and enduring impacts on cells, which could potentially rationalize the disparity in cancer rates between the genders. Additionally, the gender factor appears to be a critical determinant of survival rates for specific types of cancer, with females often exhibiting a more favorable prognosis than males in most cancer cases[2-4]. While our knowledge of the underlying molecular mechanisms is still limited, there is a growing recognition of the importance of considering the impact of gender on cancer outcomes[2-4].

Cancers involving the digestive system are a major cause of global cancer-related mortality. Currently, extensive endeavors are being made to understand the cellular and molecular processes involved in the development and progression of digestive system cancers with an aim to improve the prevention,

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early detection, and tailored therapy for these malignancies. It has been noted that the incidence of digestive system cancers, including liver, pancreatic, esophageal, gastric, and colorectal carcinoma, is generally lower in females compared to males (**Figure 1**)[1]. This observation suggests a potentially protective effect of estrogen, a prominent sex steroid hormone, on the development of digestive system cancers. Additionally, this notion underscores the significance of acknowledging gender disparities in research and the formulation of personalized treatment strategies for digestive system cancers.

Intrigued by the advances in recent years and recognizing the importance of estrogen and estrogen receptors (ERs) in digestive system cancers, we conducted this comprehensive review with a focus on understanding the sexual dimorphism in the major types of digestive system cancers. The findings shed light on the intricate roles of estrogen and ERs in digestive system cancers as well as implications for the development of tailored treatment approaches for patients with digestive system cancers, ultimately leading to improved clinical outcomes for affected individuals.

Estrogen, ERs, and estrogen signaling pathways

Estrogens are the main female hormones and the levels are higher in women of reproductive age. Of note, estrogens are present in both genders. There are three naturally occurring estrogens produced by the female adrenal cortex and ovary[5,6]. Among females of reproductive age, 17β-estradiol (E2) is the

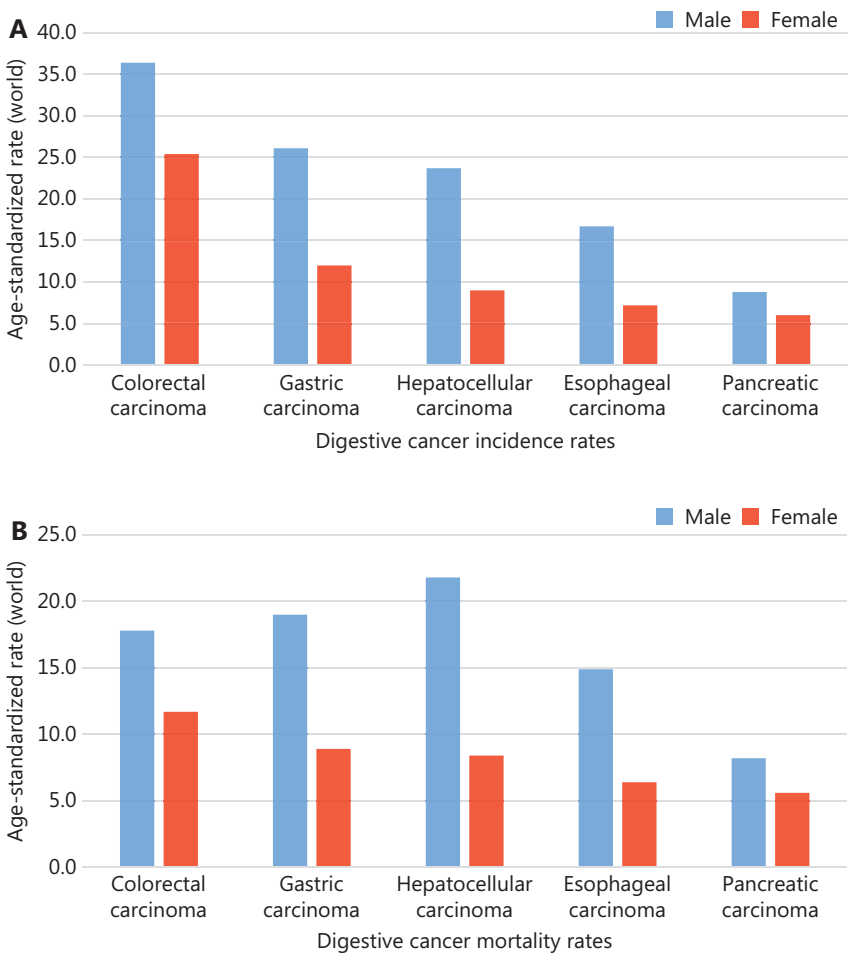

Figure 1 Incidence and mortality rate of digestive system cancers by gender. (A) Age-standardized incidence of digestive system cancers per 100,000 males (blue columns) and per 100,000 females (red columns) in 2020. (B) Age-standardized mortality rates of digestive system cancers per 100,000 males (blue columns) and per 100,000 females (red columns) in 2020. The age-standardized incidence and mortality rate for the five most common digestive cancers in both genders worldwide are presented based on the 2020 Global Cancer Statistics.

most abundant and potent estrogen[5]. Estrone (E1) is primarily produced by adipose tissue and remains relatively constant after menopause, despite the cessation of E2 production in the ovaries. Estriol (E3) is produced by the placenta during pregnancy. E2 is commonly referred to as estrogen due to its physiologic relevance during the reproductive period[5,6].

Estrogens traditionally exert their biological effects by binding to ERα or ERβ in various tissues, including the uterus, ovary, breast, liver, colon, and brain. The tissue-specific response to estrogen is primarily determined by the isoform and level of ER expression[7]. As illustrated in **Figure 2**, ERs possess conserved domains for ligand binding, DNA binding, nuclear translocation, and transcriptional activation function (AF), specifically AF-1 and AF-2. There are three isoforms of ERα, including ERα-66, ERα-46, and ERα-36. ERα-66 is the traditional variant of ERα, consisting of six distinct regions [A–F] (**Figure 2A**)[7,8]. ERα-66 acts as a transcription factor that relies on ligands to regulate gene expression through its interaction with estrogen response elements (EREs). ERα-46 lacks the A/B region responsible for encoding the transcription activation domain (AF-1) but still binds to EREs and forms heterodimers with ERα-66[9,10]. ERα-36 lacks the AF-1 and AF-2 domains but retains the DNA- and ligand-binding domains as well as the hinge region. ERα-36 has a distinctive C-terminal domain that potentially facilitates rapid estrogen signaling[11,12]. These isoforms exhibit distinct characteristics in various cancer types. It is worth mentioning that most publications utilize the term "ER" or "ERα" to specifically refer to the ERα-66 isoform because ERα-66 was the initial isoform of ER that was discovered. ERβ is another component of ER that is composed of six regions, including the A–F domains. ERβ differs from ERα primarily by the presence of a comparatively short amino-terminal domain and shares only 36% homology in the hinge region (**Figure 2B**)[10]. In addition to the traditional

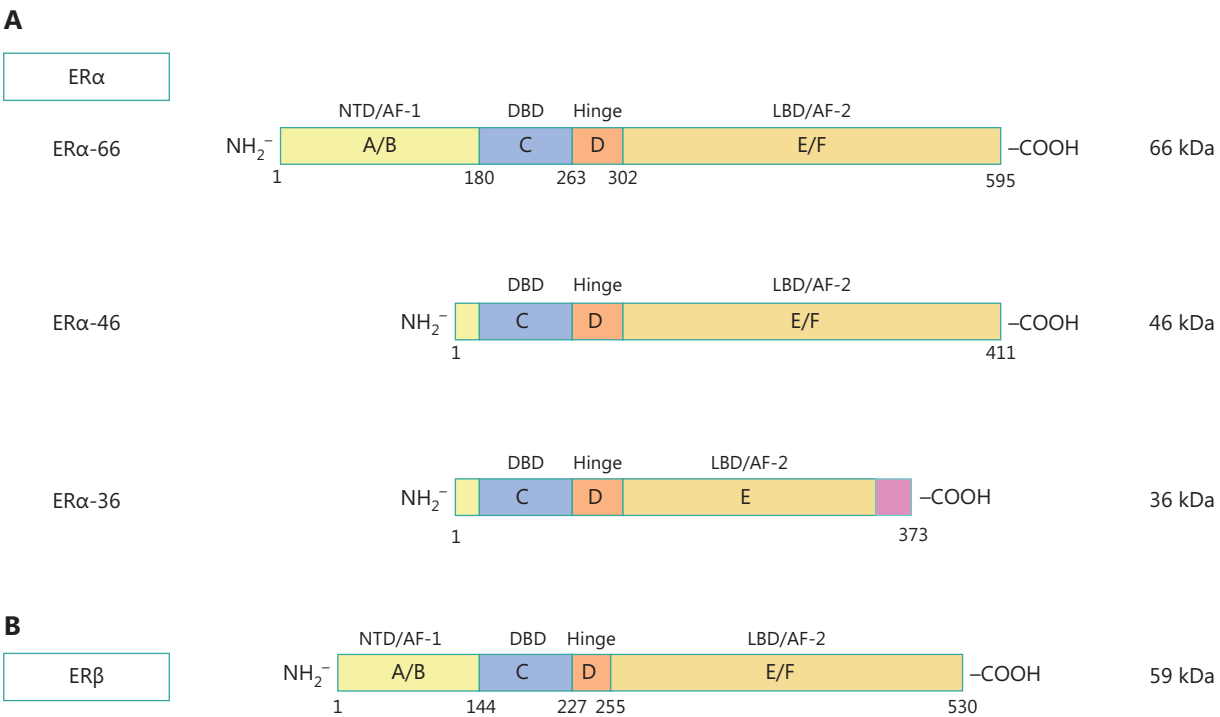

Figure 2 Schematic illustration of the structural and functional domains of the major estrogen receptor subtypes. (A) The three main isoforms of ERα (ERα-66, ERα-46, and ERα-36). ERα-66 consists of the following six structural domains, which are also functional domains based on the functions or activities which are carried out: A/B domain or amino-terminal domain (NTD/AF-1); C domain or DNA-binding domain (DBD); D domain (hinge region); and E/F domain or ligand-binding domain (LBD, AF-2). The "D" domain, located after the DBD, serves as a hinge region, contains a nuclear localization signal that is unmasked upon ligand binding, and acts as a flexible region connecting the DBD and LBD. The carboxy-terminal E/F region, also known as the LBD, contains the estrogen-binding sites and binding sites for co-activators and co-repressors. The last 27 amino acids of ERα-36 at the C-terminus are denoted by a pink box; (B) Six different structural domains of ERβ. These structural domains also serve as functional domains. AF, activation function; ERα, estrogen receptor alpha; ERβ, estrogen receptor beta.

ERs (ERα and ERβ), several novel ERs have been identified, such as G protein-coupled estrogen receptor (GPER). Unlike ERα and ERβ, GPER has a distinct structure and belongs to the 7-transmembrane-spanning G protein-coupled receptor family. GPER is involved in facilitating the rapid cellular responses to estrogen, including activation of second messengers, kinases, and ion channels[13,14]. GPER has been implicated in cancer progression and is an area of active research.

The interaction between estrogen and ERs leads to alterations in cellular functions through genomic and non-genomic pathways (**Figure 3**)[7,15]. In the genomic pathway estrogens bind to ERs in the nucleus, activating or repressing target gene expression through EREs[15,16]. This process involves the recruitment of co-regulatory proteins and subsequent modulation of target gene transcription. ERα and ERβ also regulate the transcription of some genes through indirect DNA binding without relying solely on EREs. This finding explains why approximately one-third of estrogen-induced genes lack functional EREs. Notably, ERs interact with various non-ERE DNA-bound transcription factors, including activator protein 1, specificity protein 1, forkhead box, and nuclear factor kappa B (NF-κB)[15-17].

Estrogen can also rapidly activate the intracellular signal transduction cascade through the non-genomic pathway

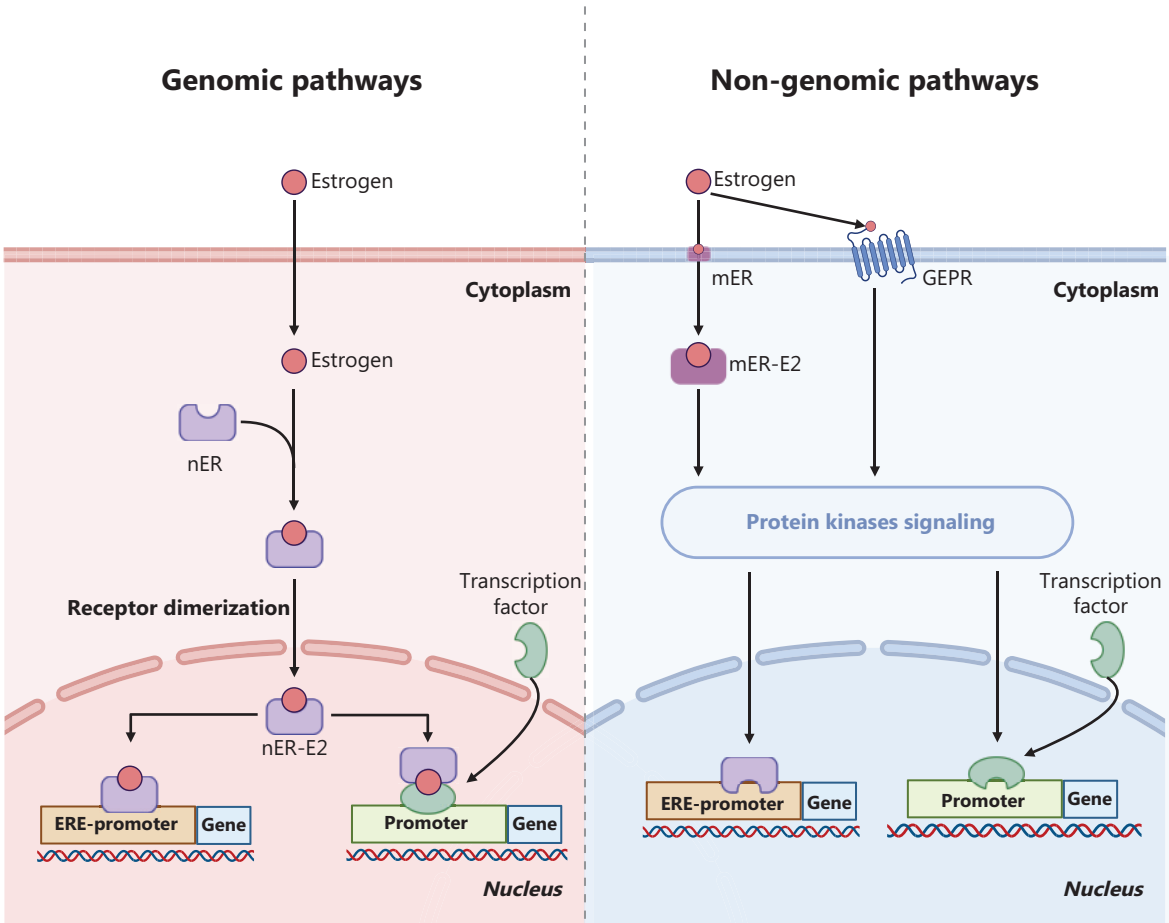

Figure 3 The genomic and non-genomic pathways of estrogen signaling. The genomic pathway involves estrogen (E2) entering the plasma membrane and binding to nuclear ERs (nERs), which results in receptor dimerization and translocation into the nucleus to induce transcriptional changes in estrogen-responsive genes with or without the presence of EREs. In the ERE-dependent signaling route, E2-ER interacts with EREs on DNA to regulate gene expression. In the ERE-independent signaling pathway, the modulation of responsive gene expression occurs through co-regulatory proteins and E2-ER modulates gene expression through interaction with transcription factors that are bound to their cognate-responsive elements on DNA. The non-genomic pathway refers to estrogen binding to membrane ERs (mERs), including G protein-coupled estrogen receptor (GPER), which induces and activates cytoplasmic events, such as intracellular signal transduction cascades and transcription factors, leading to rapid cellular responses. ER, estrogen receptor; ERE, estrogen response element.

by interacting with the ER or by binding to other non-ER plasma membrane-associated estrogen-binding proteins (**Figure 3**)[18,19]. The primary mediators of non-genomic pathways are the recently discovered membrane estrogen receptors, including GPER and ERα-36. Activation of membrane ERs by estrogen leads to rapid cellular responses, such as elevated calcium or nitric oxide levels, and the activation of various intracellular kinase cascades, including mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K), protein kinase A, and protein kinase C. Crosstalk between the genomic and non-genomic pathways has been described[7,15]. The ERs, pathway-associated proteins, and molecular effectors in both genomic and non-genomic pathways interact with each other, resulting in variations in the transcriptional activity of specific tissues and physiologic processes. These pathways form intricate, bidirectional, and versatile estrogen signaling pathways.

Roles of estrogen and ERs in digestive system cancers

Hepatocellular carcinoma (HCC)

HCC, accounting for approximately 90% of liver cancer cases, is a formidable global health challenge. Notably, males typically experience HCC rates that are 2–4 times greater than females[1,20]. This difference indicates the significant influence of sex hormones on the development of HCC in humans[17,21]. The basis for the gender disparity in HCC has not been established. However, emerging evidence has indicated that estrogen and ERs have a role in the pathogenesis of HCC. For example, previous animal studies in rodents have provided evidence that sex hormones influence the occurrence of liver cancer[22,23]. Further research has demonstrated that ERα-mediated estrogen signaling and androgen receptor-mediated androgen signaling exert major but opposite effects on HCC in females and males, respectively. Moreover, Li et al.[23] discovered that the protective effects of ERα and the facilitating effects of androgen receptor in diethylnitrosamine (DEN)-induced hepatocarcinogenesis in mice depend on Foxa1/2. In a study examining the susceptibility of HCC in mice lacking ERα, female mice without Esr1 showed a significantly greater degree of hepatocarcinogenesis when exposed to the carcinogen, diethylnitrosamine (DEN)[24]. Interleukin-6 (IL-6) has also been reported to play a crucial role in maintaining hepatocyte homeostasis[25]. Nevertheless, IL-6 facilitates the development of liver cancer through various stages[26,27]. DEN leads to tumor formation by IL-6-mediated liver damage and compensatory hyperplasia. Additionally, DEN has been shown to primarily stimulate the synthesis of IL-6 in Kupffer cells *via* MyD88. Interestingly, E2 suppresses the release of IL-6 in liver Kupffer cells, thereby diminishing hepatocyte harm and malignant growth caused by DEN[28]. These findings suggest that estrogen signaling may have a protective role in the development of HCC by modulating the IL-6 signaling pathway.

It is well-recognized that chronic hepatitis B virus (HBV) infection is a common cause of HCC, with males and postmenopausal females having a higher risk of developing HBV-associated HCC compared to younger females[29]. This finding suggests a potential influence of sex hormones, including estrogen and androgen, on HBV-associated HCC. Androgen signaling promotes HBV gene replication and transcription, while estrogen has a protective effect by reducing HBV RNA transcription and inflammatory cytokine levels[29,30]. Females with HBV infection usually have lower viral loads than males, which reduces the risk of liver cancer. Estrogen represses the transcription of HBV genes by upregulating ERα[31]. Additionally, estrogen regulates IL-6 production by Kupffer cells and STAT3 signaling, which helps control inflammatory mediators and thereby hinders the development and progression of HBV-related HCC[28,32]. According to a case-control study, estrogen has a protective effect against HCC and females who were treated with estrogen had a reduced risk of developing HCC, including hepatitis-associated HCC[33]. Hepatocellular adenoma (HA) is a rare benign tumor that typically occurs in young women with a history of prolonged oral contraceptive use. The development of HA is closely linked to the intensity and duration of contraceptive use[34]. Additionally, these tumors are also associated with the use of anabolic steroids, which may explain the increasing incidence of HA in men, especially in the presence of obesity and metabolic syndrome[35,36]. The malignant transformation from HA-to-HCC is more common in males[37]. However, females with prolonged exposure to high estrogen levels, such as occurs with extended oral contraceptive use, are at an increased risk of HA progressing to malignancy[38,39]. Both estrogen and androgen imbalances are recognized as risk factors for HA[40]. Estrogen, acting through its nuclear receptor (ERα), upregulates the expression of sigma receptor 1, a protein involved in hepatocyte proliferation and steatosis, which may be critical in the phenotype of HA associated with HNF1α mutations[41].

Moreover, disruptions in estrogen metabolism may contribute to the malignant transformation of HA, potentially modulated by β-glucuronidase enzymes in the gastrointestinal tract[42].

Over the years researchers have made advances in understanding the regulatory effects of estrogen and ERs in HCC. For example, a clinical investigation demonstrated that the expression of nuclear ERα and ERβ is higher in HCC tissues compared to corresponding non-neoplastic tissues and the levels of nuclear ERα and ERβ expression in HCC tissue exhibit an inverse correlation with tumor size and clinical staging[43]. Additionally, ERα expression may have a crucial role in modulating the YAP pathway and influencing the growth and progression of liver cancer, thus highlighting the potential of estrogen-based therapies in the management and treatment of liver cancer[44]. The administration of an ERα agonist was reported to prolong the survival time and reduce the tumor load in mouse models of HCC by suppressing the Wnt/β-catenin signaling pathway[45]. Moreover, ERα overexpression with E2 treatment downregulates carbohydrate-responsive element binding protein and reduces aerobic glycolysis and cell proliferation of hepatoma cells[46]. ERα overexpression also mediates apoptosis in ERα-negative Hep3B cells by binding of ERα to specificity protein 1[47]. In addition, estrogen modulates the ERα-36/AKT/Foxo3a signaling pathway, inducing apoptosis in liver cancer cells by downregulating oxidative stress scavenger enzymes and initiating oxidative stress[48]. Furthermore, ERα is capable of inhibiting the invasion of HCC cells by modulating the ERα/circRNA-SMG1.72/miR-141-3p/gelsolin signaling pathway[49]. Despite the expression of ERβ in HCC cells, ERβ function has not been studied as thoroughly as ERα function. It has been reported that E2 suppresses the growth of HCC cells through inhibition of tumor-associated macrophages *via* ERβ[50]. In another study E2 was shown to effectively diminish the malignant activity of HCC cells by enhancing the expression of NLRP3 inflammasomes *via* the ERβ/MAPK signaling pathway[51]. E2/ERβ has also been shown to inhibit proliferation and induce apoptosis of Hep3B cells by downregulating peroxisome proliferator-activated receptor alpha gene expression[52].

Several studies have reported a significant reduction in GPER expression in HCC tissues compared to adjacent normal tissues[53,54]. For example, GPER-positive HCC patients have significant associations with female gender, HBsAg negativity, small tumor size, a low serum alpha-fetoprotein level, and longer overall survival compared to GPER-negative patients. Moreover, activation of the GPER/epidermal growth factor receptor/extracellular signal-regulated kinase (ERK) signaling pathway using the GPER-specific agonist, G1, reduces the viability of HCC tumors. A clinical analysis suggested that simultaneous high expression of GPER and phosphorylated ERK predicts improved prognosis for HCC patients. These convergent findings indicate that targeting the GPER/ERK axis could be a potential therapeutic approach for HCC[54]. Additionally, in a mouse tumor model induced by DEN, the absence of GPER greatly enhanced the development of liver tumors through the promotion of inflammation and fibrosis, suggesting that GPER may suppress the occurrence of HCC tumors by regulating inflammatory reactions[53].

Estrogen and ERs have crucial roles in the pathogenesis and progression of HCC. In the future, specific agonists targeting these receptors could hold significant potential for the clinical treatment of HCC. However, anti-estrogen therapies, such as tamoxifen, have not yielded satisfactory results in treating HCC. This finding may be due to the primary molecular target being ERα-66, which is typically expressed at low levels in HCC[15]. Conversely, ERα-36 has a tumor-promoting effect in HCC and is highly expressed in cirrhotic and HCC tissues[55]. Thus, antagonists targeting ERα-36 are expected to become a novel therapeutic approach for HCC. Epigallocatechin-3-gallate, a natural compound with potential anticancer properties, has shown a dose-dependent inhibitory effect on HCC cells that highly express ERα-36[56]. Epigallocatechin-3-gallate activates the expression of phosphorylated ERK and caspase-3 by inhibiting the ERα-36/epidermal growth factor receptor/human epidermal growth factor receptor 2 feedback loop and the PI3K/Akt and MAPK/ERK pathways, leading to the induction of apoptosis and inhibition of proliferation in HCC cells[56].

Pancreatic carcinoma (PC)

PC is a devastating malignancy and has a higher incidence in males compared to females[1]. Previous studies have indicated that females who undergo hormone replacement therapy (HRT), specifically estrogen-only treatment, have a reduced risk of developing PC[57,58]. It has been hypothesized that female steroid hormones have a protective role in PC risk. Additionally, combining E2 with chemotherapeutic drugs has been shown to enhance the chemosensitivity of PC cells[59]. The role of ERs in pancreatic ductal adenocarcinoma (PDAC) is largely unknown. While some reports have revealed the presence of ERα and ERβ in primary PDAC[60,61],

other investigations have failed to detect ERα[62,63]. Notably, the expression of ERβ in PDAC appears to correlate with a poor prognosis[60,61].

In addition to ERα and ERβ, GPER may have a crucial role in inhibiting cancer growth in PDAC. Studies have shown that elevated GPER levels are associated with improved survival in PDAC patients. Notably, GPER agonists, such as G1 and tamoxifen, have emerged as promising candidates for PDAC treatment, opening new avenues for therapeutic intervention[64,65]. For example, Natale et al.[64] demonstrated that the GPER agonist, G1, hindered the growth of PDAC, reduced the expression of c-Myc and programmed death ligand 1, and enhanced the immunogenicity of tumor cells through GPER activation. Moreover, systemic administration of G1 is well-tolerated in mice with PDAC, resulting in tumor regression, a significant increase in survival time, and an enhancement of the effectiveness of PD-1-targeted immune therapy. Furthermore, activation of GPER has been shown to inhibit the proliferation and migration of PDAC cells[66]. Chrysin, a natural compound, has also been shown to have inhibitory effects on PDAC cells through GPER activation[66]. These findings highlight the potential therapeutic implications of targeting GPER in PDAC. Furthermore, CXC chemokine receptor 4 (CXCR4), another GPER, undergoes receptor internalization and recycling upon stimulation by its ligand, CXC chemokine 12. Blockade of CXCR4 promotes T-cell infiltration into tumors and synergizes with anti-PD-1 therapy in PDAC mouse models. Additionally, motixafortide, a CXCR4 antagonist, was evaluated in a phase IIa clinical trial (NCT02826486) for metastatic PDAC, showing favorable outcomes with respect to objective response rate, overall survival, and disease control rate[67].

PDAC is characterized by the formation of a dense stroma surrounding the carcinoma (i.e., desmoplasia). This stromal environment has a crucial role in regulating the behavior of pancreatic tumors. However, the presence of this stroma poses significant challenges for conventional chemotherapeutics and emerging immunotherapeutic agents because the stroma hinders the effective delivery of drugs to cancer cells, ultimately leading to the devastating consequences of the disease[68]. Therefore, targeting the tumor stroma represents a promising strategy for the treatment of PDAC. Interestingly, tamoxifen has been shown to regulate remodeling of stromal tissue and the microenvironment of fibrovascular tumors in PDAC tissues. This regulation was achieved through modulation of key extracellular matrix-modifying enzymes, such as lysyl oxidase homolog 2 and matrix-metalloproteinase 2, *via* the GPER/hypoxia-inducible factor-1 alpha axis[69]. Moreover, tamoxifen has been shown to inhibit the differentiation of pancreatic stellate cells into myofibroblasts by activating GPER/RhoA signaling, resulting in reduced collagen accumulation and macrophage infiltration in the tumor microenvironment[70,71]. These findings underscore the significance of the non-traditional estrogen signaling pathway in inhibiting tumor growth in PDAC. As a key regulator of the tumor microenvironment, activated GPER has shown potential in inhibiting the proliferation and growth of PDAC tumor cells as well as enhancing the efficacy of immunotherapy.

Esophageal carcinoma (EC)

The International Agency for Research on Cancer has reported a significant disparity in the incidence and mortality rate of EC between males and females, with higher rates observed among males[1]. Specifically, a meta-analysis has shown that estrogen has the potential to reduce the likelihood of developing EC in females. Furthermore, HRT has been reported to be negatively associated with the risk of EC[72]. These findings highlight the potential impact of gender and related hormonal factors on the development and progression of EC.

Histopathologically, EC is classified into two main types [esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EA)]. Interestingly, female ESCC patients with higher serum E2 levels have a more favorable prognosis[73]. This result suggests that the concentrations of sex steroid hormones may explain the gender disparity observed in ESCC. In addition, studies have shown that E2 hinders the proliferation and migration of cells associated with ESCC. However, this inhibitory effect was not observed in EC cells that do not express ERα, also referred to as ERα-negative EC cells[74,75]. These findings suggest that the presence of ERα may be required for E2 to exert its inhibitory impact on ESCC cells.

It has been reported that estrogen has a role in inhibiting ESCC growth by promoting the ER-calcium signaling pathway and this effect is attenuated by an ER antagonist[76]. Nevertheless, there is inconsistency across studies regarding the expression of ERs in ESCC. For example, Zuguchi et al.[77] detected ERα and ERβ in the nuclei of ESCC cells (41.1% and 97.8%, respectively). Similarly, high expression of ERβ in carcinoma cells is significantly correlated with unfavorable clinical outcomes in ESCC patients[77]. In contrast, Dong et al.[78] reported that the presence of ERα is inversely correlated with

the extent of tumor infiltration and results in a more favorable prognosis compared to ESCC patients lacking ERα expression. Additionally, Nozoe et al.[79] reported cytoplasmic expression of ERα in 64.4% of tumor tissues and nuclear expression of ERβ in 28.8% of tumor tissues. According to Nozoe et al.[79] the presence of ERα and the absence of ERβ are unfavorable predictors in ESCC prognosis. To date, there have been limited studies focusing on GPER in esophageal malignancies. However, a study revealed that overexpression of GPER in ESCC is associated with a negative prognosis. Therefore, GPER may contribute to cell proliferation and metastasis through activation of the p38-MAPK pathway[80].

Of the two major types of EC, EA is a rapidly increasing disease with limited treatment options. In Western countries, EA is 5–10 times more prevalent in males than females[81]. This gender disparity is supported by the U.S. registry data, which shows an overall male-to-female EA incidence ratio of 7.66[82]. Gastroesophageal reflux disease (GERD) is a significant risk factor for EA and the incidence of GERD is increasing. The progression from GERD to EA often involves the development of Barrett's esophagus[83]. Notably, males exhibit a higher susceptibility than females to developing erosive esophagitis and its associated complications, such as Barrett's esophagus and cancer[84]. Several studies have demonstrated that estrogen can bind to ERs, initiating signaling pathways that mitigate inflammation-induced damage in esophageal tissue[85,86]. Furthermore, estrogen enhances the expression of occludin and tight junction proteins, which reinforce cell adhesion between adjacent esophageal cells, thereby protecting the esophageal mucosa[87]. Consequently, HRT or interventions aimed at modulating estrogen levels and the associated signaling pathways may offer potential benefits in alleviating GERD-induced damage to the gastrointestinal epithelium, reducing esophageal inflammation, and preventing subsequent complications, ultimately helping to avert the development of Barrett's esophagus and EA[88,89]. Moreover, meta-analyses involving female patients have shown that the use of external estrogen, including HRT and oral contraceptive pills, is associated with a reduced occurrence of EA[90]. Another study indicated that ever-users of HRT have a lower occurrence of EA compared to females who have never used HRT[91]. Furthermore, the levels of circulating androgens and estrogens have been assessed in males with EA compared to matched controls. Males with higher levels of E2 have a decreased likelihood of developing EA, suggesting that a potential protective role of estrogen in males[92].

ERα and ERβ expression has been demonstrated in EA[93-95]. Notably, the expression of ERβ has been reported to increase as the lesions progress from non-dysplastic Barrett's esophagus to different levels of dysplasia and eventually invasive malignancy[96]. In cell culture models of EA, both estrogen and ER modulators (tamoxifen and raloxifene) induce cell cycle arrest and apoptosis[95,97]. Furthermore, research has explored the potential of combining ER modulators with current chemotherapy treatments. For example, the combination of cisplatin and 5-fluorouracil along with 4-hydroxytamoxifen exhibit enhanced cytotoxic effects, suggesting compatibility between ER modulator therapy and standard treatment regimens[94]. Additionally, EA cells with different ER isoforms exhibit varying cytotoxic responses to tamoxifen, with certain ER species (ERα90, ERα50, and ERα46) showing a positive response and others (ERα74, ERα70, and ERβ54) lacking a cytotoxic response[98]. These findings indicate that the presence of different ER types in EA cells potentially open up new avenues for targeted treatment in specific individuals.

Gastric carcinoma (GC)

Recent cancer statistics have reported that GC is approximately twice as common in men compared to women[1]. However, the likelihood of developing GC appears to be similar among postmenopausal women and men[99]. Several studies have demonstrated that individuals who undergo menopausal hormone therapy have a reduced risk of developing GC, mainly attributable to a protective effect of estrogens against GC[91,100]. Animal studies have further supported this finding, showing that female rats, castrated male rats, and male rats treated with E2 exhibit a lower incidence of GC compared to untreated male rats when exposed to the carcinogen, *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine[101]. In addition, untreated male rats have higher rates of morbidity due to GC compared to castrated or estrogen-treated male rats[101]. These findings suggest the potential role of estrogens in preventing GC.

The presence of ERα and ERβ has been reported at both the cellular and tissue levels in GC. Interestingly, there was no significant difference in the rate of ER-positivity between male and female GC patients. The expression of ERα (specifically, ERα-66) has been observed in approximately 20%–30% of human GC cases. At the mRNA level, there was no significant difference in ERα expression between GC tissues and matched normal tissues. However, the presence of ERα-positive expression is associated with worse overall survival[102]. Despite these

findings, a previous study on well-established cellular strains has shown variability in the results[103]. This study demonstrated that an excessive presence of ERα effectively suppresses the proliferation of MKN28 GC cells by reducing the expression of β-catenin[103]. These results suggest that the role of ERα in GC may be complex. Until now, there have been no reports on ERα-46 in GC, although efforts have been made to explore the clinical roles of ERα-36 in GC. The expression of ERα-36 is significantly elevated in human GC, which is associated with the occurrence of lymph node metastasis, indicating its potential as a prognostic indicator for lymph node metastasis in GC[104]. Tumor specimens have also shown elevated levels of ERα-36 mRNA compared to corresponding normal tissues and established GC cell lines have displayed the presence of both ERα-36 mRNA and protein. Furthermore, the ERα-36 protein is predominantly detected on the plasma membrane and in the cytoplasm of these GC cells[104]. Given the unique attributes of this recently discovered isoform, further investigations have been carried out to understand the mechanisms associated with ERα36 in GC. For example, it has been shown that increased ERα-36 expression in human GC enhances the malignant proliferation of GC cells through various signaling pathways[104-106]. However, the regulation of estrogen signaling in the proliferation of GC cells remains to be delineated due to limited evidence.

Ryu et al.[107] reported that 45.3% (67/148 cases) of GC tissues expressed ERβ and that the presence of ERβ is associated with several favorable clinicopathologic factors, including a lower tumor stage, Lauren's intestinal type, and negative perineural invasion. Additionally, the ERβ-positive group exhibited higher 3-year survival rates compared to the ERβ-negative group according to survival analysis. These findings suggest that the presence of ERβ in GC may have a protective effect against GC invasiveness[107]. Furthermore, ERβ expression in GC tumor tissues has been reported to be less than normal tissues, while ERβ absence was identified as an independent predictor that correlates with unfavorable overall survival[102]. These observations highlight the potential significance of ERβ as a prognostic marker and the potential role of ERβ in modulating GC aggressiveness. Nevertheless, further studies are warranted to elucidate the underlying mechanisms and to explore the therapeutic implications of ERβ in GC.

Studies have shown that GPER expression is decreased in GC tissues and that patients with lower GPER expression often have an unfavorable prognosis[108]. GPER functions as a tumor suppressor by modulating the epithelial-mesenchymal transition pathway[108]. GPER mRNA levels are notably reduced in GC tissues compared to normal tissues. Additionally, GPER expression decreases as GC progresses into more advanced stages, as demonstrated by the fluorescence intensity of GPER in cancer stages I and II (45% and 30%, respectively) compared to stages III and IV (25% and 20%, respectively)[109].

Treatment with the GPER agonist, G1, has been shown to attenuate GPER expression in GC. In addition, in a mouse xenograft model, increased GPER expression has been shown to enhance the antitumor effects of G1, leading to increased cell death in human GC cells. This effect is mediated by elevated levels of cleaved caspase-3, caspase-9, and cleaved poly-ADP-ribose polymerase[109]. Interestingly, GPER is activated by agonist-induced apoptosis in GC cells through activation of pERK-mediated endoplasmic reticulum stress. These findings suggest a promising paradigm in GC therapy[109]. However, the therapeutic significance of ERα and ERβ in GC remains limited until ERα and ERβ roles are more fully elucidated.

Colorectal carcinoma (CRC)

CRC, the second-leading cause of cancer-related deaths globally, is more prevalent in males than females[1]. Young females (18–44 years of age) diagnosed with CRC tend to have better survival outcomes compared to males in the same age group or older females (>50 years of age), indicating a global variation in CRC occurrence and survival based on gender[110,111]. Both epidemiologic and RCTs have demonstrated that postmenopausal females who receive HRT have significantly reduced rates of CRC compared to age-matched females who do not take HRT[112,113]. These results indicate a potential protective role of estrogen in the development of CRC.

ERα and ERβ are present in normal colorectal tissue, with ERβ being more prevalent. However, as adenomas and CRC progress, an alteration in the proportion of these two receptors has been observed; specifically, there is a decrease in ERβ and an elevation in ERα expression. In males with colon cancer the ERα levels have been shown to rise, while the ERα levels remain unchanged in females[114]. Low or absent ERβ expression has been associated with a poor prognosis in patients with CRC[115,116]. Notably, a significant decrease in ERβ has been observed in adenomatous tissue compared to normal mucosa[117], suggesting a significant reduction in ERβ expression in the precancerous phase of colon

carcinogenesis. In a report by Principi et al.[118], colorectal tissue samples from patients with long-standing ulcerative colitis were analyzed. The samples were categorized based on the degree of tissue dysplasia, ranging from non-dysplastic ulcerative colitis to low-grade dysplasia/high-grade dysplasia and colitis-associated carcinoma. This study found a progressive decline in the expression of ERβ as the severity of dysplasia increased. Another study by Stevanato et al.[119] investigated 120 individuals diagnosed with familial adenomatous polyposis (FAP)-related polyps, sporadic adenomatous polyps, or CRC. The data demonstrated that the level of ERβ expression varied among the groups with lower ERβ expression in the FAP group compared to the sporadic polyp group. Conversion of occasional polyps into cancer is associated with a significant decline in ERβ expression. T3/T4 tumors also tend to exhibit reduced ERβ expression compared to T1/T2 tumors. Of note, CRC patients with detectable expression levels of ERβ have a higher 5-year overall survival rate compared to CRC patients without detectable expression of ERβ[119]. These findings suggest that variations in ERβ expression may have a role in estrogen-mediated modification of the vulnerability to colon cancer, thus supporting the notion that estrogen may have a protective effect against the development of CRC.

ERβ has been proposed as a potential tumor suppressor in CRC. As described by Hartman et al.[120], an *in vitro* experiment was carried out to examine the molecular role of ERβ. The findings indicated that overexpression of ERβ inhibits cell proliferation and induces cell cycle arrest in the G1 phase. In addition, c-Myc, an oncogene, is highly expressed in CRC and decreased in cells with ERβ overexpression compared to control cells. Moreover, in an *in vivo* study in mice with a severe combined immunodeficiency/beige phenotype, reintroduction of ERβ led to a 70% decrease in tumor volume, which was statistically significant[120]. Similarly, a previous study in ERα-deficient HCT8 colon cancer cells also identified ERβ as a modulator of the cell cycle. It was observed that the extent of ERβ transfection directly correlates with suppression of cell growth[121]. Furthermore, ERβ has been shown to impact inflammatory signaling and suppress the development of CRC through the NF-κB subunit, p65[122]. Additionally, research in animal models has demonstrated that estrogens exert protective effects through an ERβ-dependent mechanism. For example, administration of the ERβ-selective agonist, diarylpropionitrile, to male and female $Apc^{Min/+}$ mice significantly reduces the number and size of polyps in the small intestine[123]. In a study by Son et al.[124], the addition of E2 in azoxymethane/dextran sulfate sodium (AOM/DSS) mouse models was examined for potential influence on CRC carcinogenesis. Mice treated with E2 exhibit reduced levels of inflammatory indicators and a reduced incidence of tumors compared to the untreated group. Similarly, when ovariectomized female mice were given external E2 replacement, the protective effects of E2 against AOM/DSS-induced colitis and the development of cancer were demonstrated[125]. Moreover, in the absence of Nrf2, E2 suppresses the development of CRC induced by AOM/DSS *via* enhancing ERβ-related signaling pathways[126]. These studies provide evidence suggesting that estrogen offers a novel and efficient therapeutic approach for treating CRC. Promising therapeutic approaches include the administration of external E2 and reactivation of the ERβ subtype, either individually or in combination.

Selective ER agonists stimulate the tumor suppressor function of ER in CRC. Both natural and synthetic ligands for ERβ have shown protective roles against CRC development. Genistein, an isoflavone from soy products, inhibits proliferation and promotes apoptosis by increasing the expression of ERβ followed by activation of various pathways in cancer cells[127]. Genistein has been effective in preventing and treating malignancies, including CRC[128]. Although large-scale clinical trials are lacking, calycosin, another isoflavone, has been shown to suppress CRC growth by inhibiting the ERβ-mediated PI3K/Akt signaling pathway[129]. Supplementation with Eviendep specifically induced ERβ expression in the colon mucosa. Moreover, short-term (90 d) supplementation with Eviendep in FAP patients effectively reduced polyp numbers by 32% and size by 51%, suggesting a central role for Eviendep in preventing carcinogenesis in the colon[130].

To date, the roles of GPER in the development of CRC are not fully understood[131,132]. A previous study indicated that GPER expression is significantly reduced in CRC tissues compared to adjacent normal tissues. Additionally, CRC patients with lower GPER expression have a poorer prognosis. Moreover, activation of GPER has been shown to hinder cell growth, induce cell cycle arrest, promote mitochondria-related apoptosis, and increase endoplasmic reticulum stress in CRC cells through various intracellular signaling pathways[133]. Bustos et al.[134] also reported that application of E2, facilitated by GPER, inhibits the migration and growth of CRC cells under normal oxygen conditions but stimulates CRC cells under low oxygen conditions. These results suggest that GPER function in CRC may

vary depending on the aerobic/anoxic conditions of the tumor microenvironment.

Implications, future prospects, and key challenges

The aforementioned studies provide compelling evidence supporting gender disparities in the incidence, mortality, prognosis, and response to therapy of cancer as well as implicate that estrogen has a therapeutic benefit in some types of digestive system cancers[2,3]. The male predominance in digestive system cancers and the lower incidence in females have been hypothesized to be mainly attributable to the beneficial impact of estrogen. Phytoestrogens, phenolic compounds derived from plants, have a similar molecular structure and size to vertebrate steroid estrogens, making phytoestrogens capable of mimicking vertebrate steroid estrogen effects. Soy, in particular, is rich in various bioactive phytochemicals, including isoflavones, which have been extensively studied[135]. Isoflavones, a type of polyphenol with estrogenic effects, have a similar structure to E2 and bind to ERs. However, the estrogenic activity of isoflavones is considerably lower, ranging from 1/100th to 1/1,000th that of estrogen. Depending on the circumstances, isoflavones can act as a substitute for estrogen in cases of deficiency or as an estrogen antagonist in cases of excess by blocking the ERs to which estrogen typically binds[135]. Therefore, the potential impact of consuming soy has garnered interest due to its potential to decrease the likelihood of developing digestive system cancers, such as HCC and GC[136-138]. Building upon these convergent findings, we propose that considering gender-specific approaches in cancer prevention and treatment, as well as exploring the therapeutic potential of estrogen and phytoestrogens, may enhance the management of digestive system cancers in the future.

Estrogen was initially recognized as a sex hormone that influences specific cells by activating its homologous receptors (ERs). Estrogen has a crucial role in regulating the growth and development of the human reproductive system. However, emerging evidence indicates that estrogen also significantly impacts the physiologic and pathologic processes of non-reproductive organs through an interaction with ERs[2]. Dysregulation of ERs is closely associated with the occurrence and progression of various cancers, including those of the reproductive system as well as non-reproductive cancers, such as those affecting the digestive system (**Table 1**).

Table 1 Intricate roles of estrogen receptors in cancers

Digestive system cancers	ERα	ERβ	GPER
Hepatocellular carcinoma	↓	↓	↓
Pancreatic carcinoma	–	↑	↓
Esophageal squamous cell carcinoma	↓↑	↓↑	–
Esophageal adenocarcinoma	–	–	–
Gastric carcinoma	↓↑	↓	↓
Colorectal carcinoma	–	↓	↓↑
Reproductive systems cancers	**ERα**	**ERβ**	**GPER**
Breast cancer	↑	↓	↓↑
Ovarian cancer	↑	↓↑	↓↑
Endometrial cancer	↓↑	↓↑	↓↑
Cervical cancer	↓↑	↑	↓↑
Prostate cancer	↑	↓↑	↓
Testicular cancer	–	↓	↑

ERα, estrogen receptor alpha; ERβ, estrogen receptor beta; GPER, G protein-coupled estrogen receptor. ↓, the suppression of oncogenesis; ↑, the promotion of oncogenesis; ↓↑, represents controversial functions; –, represents insufficient evidence.

The role of estrogen in digestive system cancers differs from the role in breast cancer. While estrogen is known to promote breast carcinogenesis, estrogen likely has a protective role in digestive system carcinomas, specifically in HCC, PDAC, EC, and CRC. This difference in the effects of estrogen on various types of cancers may be attributed to the selective regulation of estrogen in different cells and organs. In this review we have summarized studies investigating the involvement of estrogen and ERs in primary cancers of the digestive system (**Figure 4**). Nevertheless, the role and mechanism of ER signaling have been incompletely addressed in some cancers, with HCC and CRC being the most extensively studied. Interestingly, the clinical significance of ER-mediated signaling shows great tissue or cancer specificity, such as ERα in HCC, ERβ in CRC, and GPER in PDAC. Therefore, additional studies are warranted to gain a deeper understanding of the selective regulation of estrogen in different organs and the distinct biological functions of ER subtypes in various types of cancer, as well as to identify the most suitable receptor subtype for targeted cancer treatment.

Digestive system carcinomas continue to be a significant cause of cancer-related morbidity and mortality worldwide. Despite significant advances in treatment, the incidence of

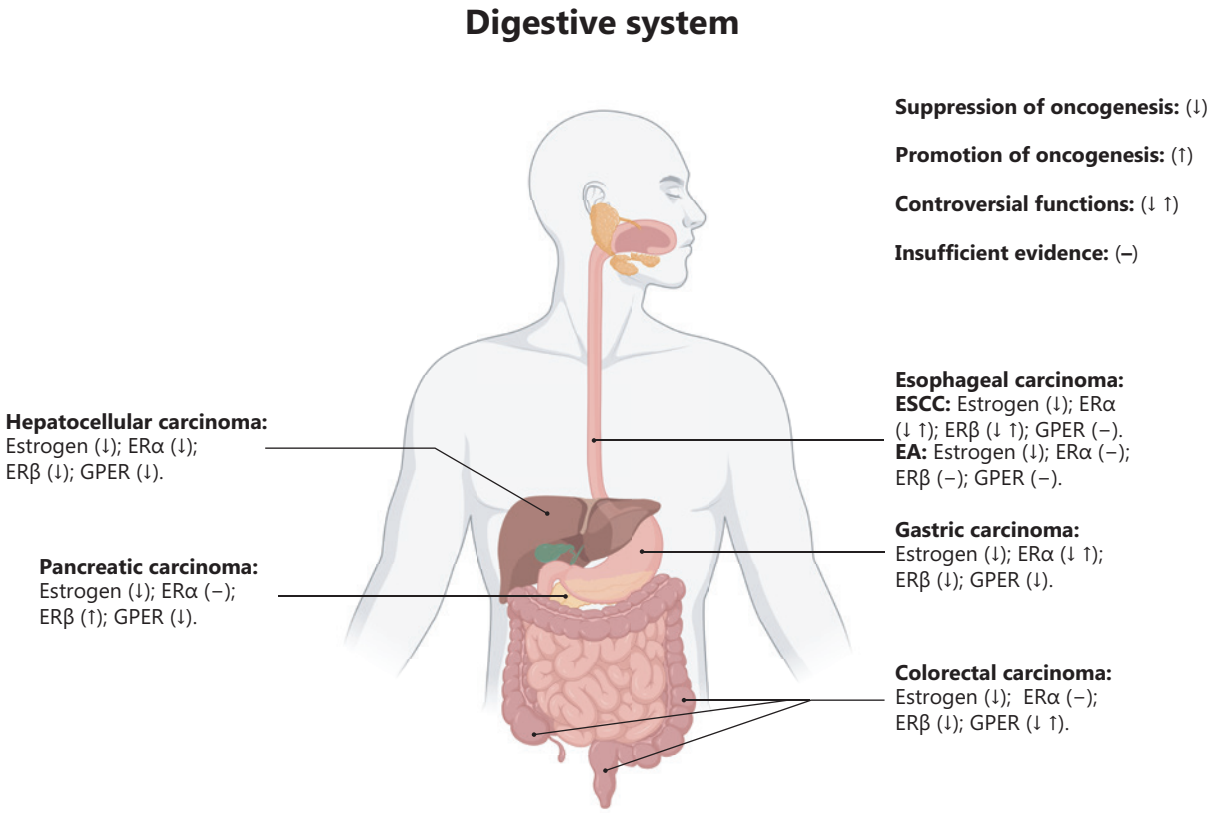

Figure 4 Role of estrogen and ERs in digestive system cancers. The varying effects of estrogen and ERs on different primary digestive system cancers have been observed, potentially due to changes in the microenvironment and selective regulation within specific organs. EA, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; ERα, estrogen receptor alpha; ERβ, estrogen receptor beta; GPER, G protein-coupled estrogen receptor. ↓, the suppression of oncogenesis; ↑, the promotion of oncogenesis; ↓↑, represents controversial functions; –, insufficient evidence.

metastasis and recurrence is on the rise mainly due to late-stage diagnosis, the emergence of drug resistance, and treatment-related adverse events. Therefore, the exploration of additional treatment alternatives is crucial. Estrogen and ERs have been implicated in the pathogenesis and progression of these digestive cancers, offering potential targets for therapeutic intervention, including selective estrogen receptor modulators, selective estrogen receptor degraders, phytoestrogens, synthetic estrogens, and synthetic compounds[139]. The use of synthetic estrogens has been shown to decrease the likelihood of HCC and CRC, as well as to inhibit cancer cell growth. Additionally, selective estrogen receptor modulators, such as tamoxifen and raloxifene, have demonstrated effectiveness in arresting the cell cycle and triggering apoptosis in EA. Moreover, ERβ agonists have demonstrated promising results in the treatment of CRC in preclinical animal models, while the specific activation of GPER may be more effective for certain cancers, such as HCC and PDAC. Thus, ER signaling could be a potential therapeutic target to improve non-surgical treatments for digestive system cancers. Understanding the roles of ERs and ER signaling pathways may pave the way for novel treatments. This review systematically explored the therapeutic targeting of ERs and ER-associated signaling pathways in these cancers (**Table 2**).

It is important to acknowledge the limitations in previous studies regarding ER expression. Furthermore, the survival prognosis has been assessed in some studies concerning the presence of ERs in PDAC, EC, and GC. Nevertheless, these studies often yield inconsistent and even conflicting results. Various factors, such as tissue processing, antigen retrieval, and antibody specificity, can complicate the detection of ER at the protein level, potentially leading to both positive and negative confounding results. For instance, antibodies may non-specifically bind to antigens unrelated to ER, resulting in false-positive results. Conversely, antibodies generated against synthetically produced peptides might attach to epitopes

Table 2 Clinical treatment and key pathways targeting estrogen and ERs in digestive cancers

Cancer type	HRT	SERMs (tamoxifen)	SERDs (fulvestrant)	Promising therapeutics	Related ERs	ER-associated pathways
HCC	↓	↓	↓	Epigallocatechin-3-gallate /GPER agonist G1	ERα-36 and GPER	ERα-36/EGFR/Her-2, PI3K/Akt and ERK/MAPK
PDAC	↓	↓	–	GPER agonist G1/Chrysin/Motixafortide	GPER	GPER/RhoA, ERK/MAPK and Wnt/β-catenin
ESCC	↓	↓	–	–	GPER	p38-MAPK
EA	↓	↓	–	–	–	PI3K/Akt
GC	↓	–	↓	GPER agonist G1	GPER	ERK/MAPK and pERK-ATF4-CHOP
CRC	↓	↓	–	Calycosin/Eviendep/Genistein	ERβ	PI3K/Akt and NF-κB

CRC, colorectal carcinoma; EA, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; ERs, estrogen receptors; GC, gastric carcinoma; ERα, estrogen receptor alpha; ERβ, estrogen receptor beta; GPER, G protein-coupled estrogen receptor; HCC, hepatocellular carcinoma; HRT, hormone replacement therapy; PDAC, pancreatic ductal adenocarcinoma; SERMs, selective estrogen receptor modulators; SERDs, selective estrogen receptor degraders; ↓, the suppression of oncogenesis; ↑, the promotion of oncogenesis; –, insufficient evidence

unseen in natural proteins or epitopes that are either hidden or absent in different ER versions, leading to false-negative results. To overcome this challenge, an evaluation using a collection of antibodies, including those specifically designed to target various ER isoforms, could be advantageous. Another challenge lies in the unclear definitions of the role and functionality of each ER isoform. Although earlier studies were conducted in cell lines expressing ERα and ERβ, the mere presence of these receptors does not necessarily indicate a role in mediating responses. To further understand the roles of ERs and ER isoforms in different cancer cells, future research would benefit from knockdown experiments, such as gene deletion using CRISPR-Cas9 technology and the utilization of tissue-specific knockout mouse models of ERs. Additionally, males and females typically have different sex chromosomes (XY for males and XX for females), that potentially result in variation of gene expression and regulation. Some genes related to cancer susceptibility may be located on the sex chromosomes or regulated differently between the genders. Furthermore, other co-regulators or epigenetic factors may be involved in the intricate regulation of estrogen signaling.

Conclusions

Gender disparities in the development of digestive system cancers are notable with females having a lower incidence of these cancers compared to males. Extensive studies in humans, animal models, and cell cultures suggest a potential protective role of estrogen in digestive system cancers, although some inconsistencies and occasional controversies persist. Moreover, the estrogen signaling pathways, consisting of estrogen and ERs, have a critical role in the gender disparities of these cancers through direct and indirect pathways, including genomic and non-genomic pathways. These pathways have distinct impacts and roles in different types of digestive system cancers, which merit attention. With the advances in precision medicine and molecular diagnostics, leveraging the estrogen signaling pathways for personalized treatment strategies in the prevention and management of digestive system cancers influenced by estrogen holds enormous promise.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

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