Review

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Current status and perspectives of molecular mechanisms of gender difference in hepatocellular carcinoma: The tip of the iceberg?

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SUMMARY: Hepatocellular carcinoma (HCC) risk factors and incidence vary globally, but men generally have higher incidence than women. Men also tend to have a worse prognosis in terms of survival period and pathological characteristics. Furthermore, there are notable gender differences in treatment strategies and drug responses. While traditional risk factors such as hepatitis B virus, hepatitis C virus, alcohol consumption, and metabolic syndrome contribute to these differences, the underlying molecular mechanisms remain partly understood. Recent research has focused on elucidating the roles of sex hormones, DNA damage and repair pathways, immune microenvironments, and genetic/epigenetic factors in driving gender-specific disparities. For instance, estrogen receptor signaling has been shown to suppress HCC progression, whereas androgen receptor signaling promotes tumor development. Additionally, immune cells such as tumor-associated macrophages and regulatory T cells exhibit gender-specific patterns, with males typically showing higher levels of immunosuppressive cells. Omics analyses, including genomics, transcriptomics, and proteomics, have further revealed sex-specific differences in gene expression, protein interactions, and metabolic pathways. Despite these advances, significant gaps remain in understanding the interplay between environmental, hormonal, and genetic factors in shaping gender disparities in HCC. Future research should prioritize the identification of novel molecular targets, the development of gender-specific therapeutic strategies, and the integration of multi-omics data to address these disparities. Addressing these challenges will be critical for improving diagnostic, prognostic, and therapeutic outcomes in HCC patients of both sexes.

Keywords: epidemiological characteristics, sex hormones, immune microenvironment, multi-omics analysis

1. Introduction

Gender differences significantly influence the incidence and mortality rates of tumors worldwide, spanning a wide range of ages and various cancer types. Research reveals that the incidence rates of hematological malignancies, as well as cancers of the bladder, colon, skin, liver, and brain, are notably higher in men than in women (*1*). Furthermore, these gender differences contribute to variations in prognoses, which are shaped not only by biological, environmental, and hormonal factors but also by differences in the immune system (*2*).

Hepatocellular carcinoma (HCC) ranks as the sixth most common tumor globally and is the third leading cause of cancer-related mortality, accounting for 865,269 new cases and 757,948 deaths annually (*3*). The primary risk factors for HCC include hepatitis B virus, hepatitis C virus, exposure to aflatoxins, alcohol consumption, smoking, obesity, and diabetes (*4*). The incidence of HCC is at least two to three times higher in men than in women, with a worse prognosis observed in men (*3*). This gender disparity is attributed not only to differences in sex hormones but also to an unequal distribution of risk factors, such as alcohol use and smoking, which are more prevalent among men.

The pathogenesis of HCC involves intricate molecular and immune processes. Recent research has underscored the pivotal roles of various immune cells and signaling pathways within the tumor microenvironment of HCC. Tumor-associated macrophages (TAMs) display notable heterogeneity and plasticity, with M2-type TAMs driving tumor progression and immune suppression through the release of anti-inflammatory cytokines, such as IL-10 and TGF-β. Similarly, regulatory T cells contribute to immune homeostasis by inhibiting T-cell activation, thereby dampening anti-tumor immune responses. Additionally, myeloid-derived suppressor cells amplify immune suppression by restraining the functional activities of T cells and natural killer cells (*5,6*).

The goal of this review is to explore the factors

influencing sex-based differences in the incidence and prognosis of HCC, delve into the current understanding and future perspectives of the molecular mechanisms underlying these differences, and discuss the clinical implications that contribute to this heterogeneity.

2. Epidemiological Sex Differences in HCC Incidence and Prognosis

2.1. Sex Differences in HCC Incidence

According to statistics from the International Agency for Research on Cancer, in recent years, the global incidence and mortality rates of HCC have consistently been significantly higher in males than in females. While the magnitude of this sex difference varies across regions and ethnic groups, the overall trend remains consistent (*3*).

In East and Southeast Asia, such as China and Japan, the incidence of HCC is 2 to 3 times higher in males than in females, which is primarily attributed to hepatitis B virus (HBV) infection (*7,8*). In West and North Africa, the male-to-female ratio of HCC incidence is 1 to 2 times higher, with hepatitis C virus (HCV) and HBV infections being the main etiologies (*9,10*). In North America and Europe, the primary etiologies are alcohol use and metabolic syndrome. In the United States, the incidence of HCC in males is 3.18 times higher than in females (*11*). In Europe, the male-to-female ratio of HCC incidence ranges from 2:1 to 5:1. Notably, in countries such as France and Malta, the male-to-female ratios are as high as 5.0 and 4.8, respectively (*3*). However, in Mexico, the sex difference in HCC incidence is smaller, with a male-to-female ratio of approximately 1.4, primarily attributed to alcoholic liver disease and HCV infection (*12*). The male-to-female ratios of HCC incidence across different regions and countries are summarized in Table 1.

2.2. Sex Differences in HCC Prognosis

Significant sex differences exist in the prognosis of HCC. Females are typically older at the time of HCC diagnosis. For instance, in a multi-ethnic Asian cohort study involving 1,716 patients, the median age at diagnosis was 69 years for females, compared to 62 years for males (*13*). Another retrospective study of 1,110 patients also found that the mean age at diagnosis was 62.5 years for females, compared to 59.2 years for males (*14*).

Males have shorter overall and disease-free survival than females. In the aforementioned retrospective study of 1,110 patients, the median overall survival was 17.1 months for females versus 12.0 months for males[19]. Additionally, in a single-center study of patients with unresectable HCC, the median survival was 14 months for females and 9 months for males (*15*). Males also have higher HCC recurrence rates and shorter disease-free survival. One study showed that the median disease-free survival was 19.5 months for females versus 4.5 months for males (*16*).

Males with HCC exhibit higher malignancy than females. In the cohort of 1,716 patients, males presented with more advanced tumor stages at diagnosis, with 39.7% of females versus 28.4% of males in BCLC stage 0/A. Males had a higher incidence of distant metastasis (11% *vs.* 7.7% in females) and portal vein tumor thrombosis (33.4% *vs.* 19.4% in females). Additionally, males had a higher incidence of multifocal lesions (39.5% *vs.* 30% in females) (*13*).

Overall, males typically have a worse prognosis than females in HCC, with differences observed in age at onset, overall survival, recurrence rate, disease-free survival, and tumor characteristics (Table 2).

3. Sex differences in therapeutic strategy and drug response of HCC

3.1. Sex differences in therapeutic strategy

Sex differences exist in healthcare utilization and treatment adherence for HCC. Females are more proactive in utilizing healthcare resources, such as engaging in preventive services like liver cancer screening, which may be attributed to their generally higher health awareness and willingness to undergo medical check-ups. In contrast, males tend to seek medical care only when the disease progresses to more advanced stages (*17*). Additionally, females tend to show better adherence to medical advice during treatment, such as taking medications as prescribed and attending

Table 1. Etiologies and male-to-female incidence ratios of HCC across different regions and countries

Region	Country	Main etiology	Male-to-Female Incidence Ratio
Asia	China	HBV	2.71
	Japan	HBV	2.14
West and North Africa	Gambia	HBV	1.56
	Egypt	HCV	1.50
North America	USA	Alcohol and metabolic syndrome	3.18
Europe	France	Alcohol and metabolic syndrome	5.0
	Malta	Alcohol and metabolic syndrome	4.8
South America	Mexico	Alcoholic liver disease and HCV infection	1.4

Table 2. Gender Differences in the Prognosis of HCC

Prognosis Factor		Male	Female
	Median age at onset (years)	62	69
Survival time	Median overall survival (months)	12.0	17.1
	Disease-free survival (months)	4.5	19.5
Pathological characteristics	BCLC stage 0/A rate	28.4%	39.7%
	Distant metastasis rate	11%	7.7%
	Vascular invasion rate	33.4%	19.4%
	multiple lesion rate	39.5%	30%

regular follow-ups, which helps improve treatment outcomes and prognosis. In contrast, males may have poorer adherence due to reasons such as busy work schedules or insufficient emphasis on treatment (*14*).

Sex differences also exist in the selection of HCC treatment approaches. Multiple studies have indicated that females are more inclined to undergo surgical resection and ablation for HCC treatment (*18*). This may be related to females being diagnosed at earlier stages, making them more suitable for surgical treatment. Early access to effective treatment may be one reason why females have a better prognosis than males with HCC.

3.2. Sex differences in drug response

Females exhibit higher blood drug concentrations and longer drug elimination times in chemotherapeutic pharmacokinetics, which may be related to lower drug clearance capacity and higher drug exposure levels (*19*). A clinical trial with over 23,000 patients found that females had a 34% higher risk of severe toxicity when receiving immunotherapy, targeted therapy, or chemotherapy (*2*). Conversely, due to lower drug clearance rates in females, chemotherapeutic agents may remain in the body for a longer period, potentially leading to better therapeutic outcomes (*19*).

Estrogen-related drugs have been confirmed to have a protective effect on HCC. A study of over 3,000 HCC patients in China found that females and oral contraceptive use were associated with improved survival (*20*). Another case-control study of 234 female HCC patients found that hormone therapy was associated with improved survival (*21*). However, the use of estrogen-related drugs for HCC treatment has not yet been applied in clinical practice, and is a promising direction for future research.

4. Epidemiological risk factors in gender disparity of HCC

Gender disparities in HCC are influenced by several epidemiological risk factors, including sex hormones, alcohol consumption, smoking, metabolic states, diet, and HBV infection. These risk factors vary between genders, contributing to the observed differences in the incidence and progression of HCC (Figure 1).

4.1. Sex hormones

Recent studies indicate that sex hormones may play a pivotal role in the onset and progression of HCC (*20,21*). Furthermore, HBV-associated HCC appears to be more prevalent in men and postmenopausal women compared to premenopausal women, likely due to its close relationship with sex hormones. Broadly speaking, the androgen axis tends to promote tumor development in HCC, whereas the estrogen axis generally exerts a tumor-suppressing effect (*22*).

The estrogen pathway constitutes a signaling network involving estrogen and its related receptors, believed to have a protective role in the pathogenesis of HCC. These anti-tumor effects are thought to be mediated through various transduction pathways. Estrogen receptor α appears to inhibit HCC cell invasion by transcriptionally regulating the expression of circRNA SMG1.72, achieved by directly binding to the 5' promoter region of its host gene, SMG1 (*23*). Protein tyrosine phosphatase receptor type O has been identified as an inhibitor of JAK- and PI3K-dependent dephosphorylation signaling, as well as STAT3 transcriptional activity, thereby suppressing tumorigenesis and progression. ERα functions as a transcription factor for Protein tyrosine phosphatase receptor type O, promoting its expression and enhancing its anti-tumor activity (*24*). Additionally, within the tumor microenvironment, estrogens may act as immunoregulatory agents. Estrogen-related genes have been shown to influence immune cell infiltration and modulate the response to immunotherapy in cases of HCC.

Phosphorylation of the androgen receptor by the mechanistic target of rapamycin complex 1 promotes hepatic steatosis as well as the development and progression of HCC, both independently and synergistically with androgen (*25*). Recent findings reveal that androgen receptor (AR) variant 7 amplifies c-MYC-driven hepatocarcinogenesis by enhancing its oncogenic functions while suppressing its anti-oncogenic roles (*26*). Transcriptionally active splice variants of the AR have been shown to accelerate the progression of HCC. Furthermore, the activation of Toll-like receptor 4 (TLR4) is essential for the progression of HCC. By interacting with TLR4, the AR facilitates the development, migration, and invasion of HCC cells (*27*).

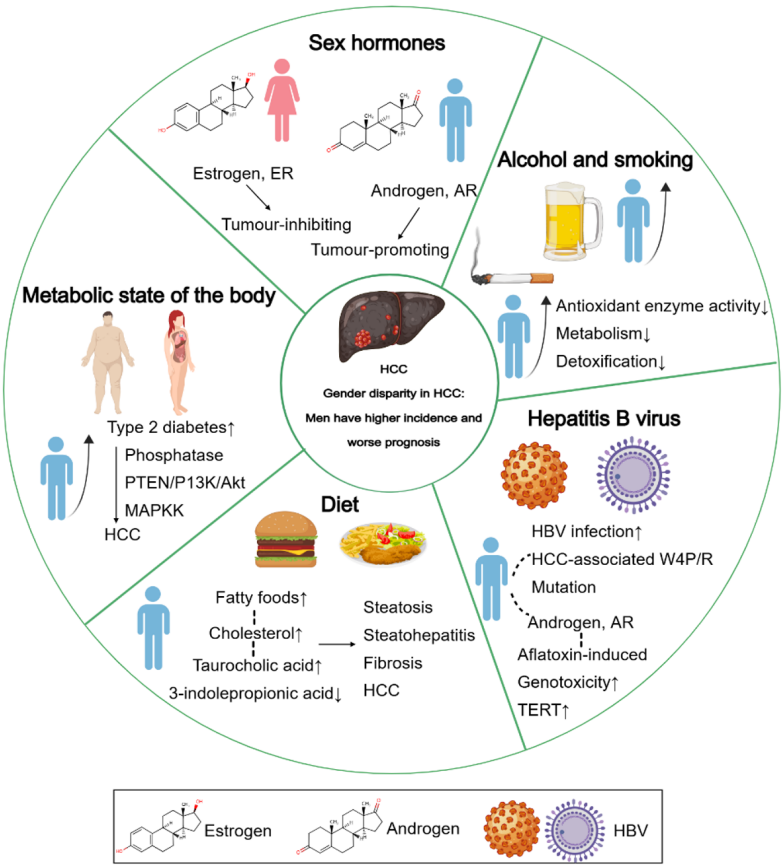

Figure 1. Epidemiological risk factors in gender disparity of HCC. Epidemiological risk factors in gender disparity of HCC include sex hormones, alcohol and smoking, metabolic state of the body, diet, and HBV. Estrogen and estrogen receptors (ER) have a tumor-inhibiting effect, while androgen and androgen receptors (AR) have a tumor-promoting effect. Men consume alcohol and smoke at higher rates than women. Among smokers, antioxidant enzyme activity in the liver of men is lower than that of women. Men's liver has weak ability to metabolize and detoxify smoking-related toxins. The incidence of type 2 diabetes in men is higher than that in women. Insulin resistance and hyperinsulinemia caused by type 2 diabetes affect the development of HCC through several molecular pathways, including phosphatase and tensin homolog (PTEN)/P13K/Akt and MAPK kinase (MAPKK). Men prefer fatty foods, which contain abundant cholesterol. Dietary cholesterol induces changes in gut bacterial metabolites, including increased taurocholic acid and decreased 3-indolepropionic acid, which can lead to the sequential progression of steatosis, steatohepatitis, fibrosis and ultimately HCC. Men are more likely to become infected with HBV. A novel HCC-associated W4P/R mutation in HBV genotype C large surface protein, found exclusively in male HCC patients. Androgen may enhance aflatoxin-induced genotoxicity and inflammation to HCC in male hepatitis B patients. HBV-integrated AR-induced telomerase reverse transcriptase gene (TERT) upregulation and point mutation in TERT promoter region identified as mechanism for male dominance of HBV-related HCC.

4.2. Alcohol and smoking

Alcohol abuse has been established as a significant contributor to HCC. Among patients with alcohol-associated cirrhosis, the annual incidence of HCC ranges from 1.3% to 3%. In 2019, alcohol was responsible for approximately 20% of global HCC-related deaths (*28*). Alcohol can cause HCC through various mechanisms, including the mutagenic effects of acetaldehyde toxicity, which leads to the formation of proteins and DNA adducts. Additionally, excessive iron deposition in the liver can lead to alterations in reactive oxygen species, lipid peroxidation, and metabolism. Inflammatory and damaged immune responses, modifications to DNA methylation, and various signaling pathways, including the gut-liver axis, can also contribute to the progression of HCC (*29*). Women are generally more susceptible to the toxic effects of alcohol than men, which may be attributed to the lower activity of alcohol dehydrogenase and aldehyde dehydrogenase in women. Women may develop severe alcoholic liver disease with comparatively lower alcohol consumption, and women are at an elevated risk of developing HCC due to alcoholic liver disease (*30*). Due to cultural, lifestyle, and economic differences, alcohol consumption patterns between genders differ across various countries and regions. Overall, men consume alcohol at significantly higher rates than women (*31*). Additionally, due to the anti-cancer effect of estrogen on HCC and the promoting effect of androgens on HCC, men are more likely to develop HCC.

Smoking is an independent risk factor for liver fibrosis and also contributes to the development of HCC. Smoking is more prevalent in men than in women in most countries (*32*). Female and male smokers exhibit distinct smoking-induced immune cell profiles in the

tumor microenvironment (*33*). Male livers have a reduced capacity to metabolize and detoxify smoking-related toxins, leading to a higher risk of HCC among male smokers. Smoking increases the risk of HCC through multiple molecular mechanisms, including DNA damage, oxidative stress, and inflammatory responses. Antioxidant enzyme activity in the liver of men is lower than in women, and DNA damage and oxidative stress caused by smoking are more significant in men (*34*). Moreover, the activities of T cells and NK cells are significantly lower in male smokers than in female smokers, resulting in decreased immune surveillance against HCC in men (*33*).

4.3. Metabolic state of the body

Metabolic syndrome is a clinical syndrome characterized by obesity, dyslipidemia, hyperglycemia, and hypertension, and is associated with an increased risk of HCC (*35*). Metabolic comorbidities have been strongly correlated with higher all-cause mortality rates in HCC patients. Notably, the risk of all-cause mortality rises significantly in HCC patients who present with two or more metabolic risk factors, such as diabetes, hypertension, or high cholesterol (*36*).

Metabolic complications, such as obesity and diabetes, are cancer-promoting factors. Although women have higher rates of obesity, obese men face a higher risk of HCC. Furthermore, men are more prone than women to develop insulin resistance and hyperglycemia in response to nutritional challenges (*37*). Research indicates that many aspects of energy balance and glucose metabolism are regulated differently between sexes, influencing susceptibility to type 2 diabetes. Globally, the incidence of type 2 diabetes is higher in men than in women, particularly among young people (*38*). Recent studies have shown that type 2 diabetes increases the risk of HCC by 2.5- to 4-fold (*39*). Moreover, patients with long-standing and poorly controlled disease seem to face a higher risk. Insulin resistance and hyperinsulinemia caused by type 2 diabetes affect the development of HCC through several molecular pathways, including the PTEN/PI3K/Akt and MAPK pathways (*40*). Insulin resistance and the insulin-like growth factor-1 signaling pathways are major contributors to the development of HCC. Insulin resistance induces inflammation, oxidative stress, DNA damage, and activates cellular pathways that promote cell growth and proliferation, thereby contributing to HCC development (*39*).

4.4. Diet

The liver plays a crucial role in the metabolism of carbohydrates, fats, and proteins. Consequently, diet has significant biological impacts on key pathways that are hypothesized to be involved in the risk of HCC. Research conducted by Peng Zhou *et al*. demonstrates that elevated levels of uridine diphospho-N-acetylglucosamine and O-GlcNAcylation, resulting from high dietary fructose intake, contribute to the progression of HCC (*41*). Małgorzata Grzymisławska *et al*. found that dietary behavior, dietary styles, and dietary profiles are associated with gender. Men prefer high-fat foods with strong flavors, primarily driven by the pleasure of eating (*42*). However, fatty foods contain abundant cholesterol. Dietary cholesterol induces changes in gut bacterial metabolites, including increased taurocholic acid and decreased 3-indolepropionic acid, which can drive the sequential progression from steatosis to steatohepatitis, fibrosis, and ultimately HCC (*43*). Yanan Ma *et al*. found a positive association between the intake of meat-derived mutagenicity or heterocyclic amines and the risk of HCC. The intake of processed red meat may be associated with a higher risk, while the intake of poultry or fish may be associated with a lower risk of HCC (*44*). There is currently limited evidence to confirm the role of diet in gender differences in HCC, and further research in this area is warranted.

4.5. Hepatitis B virus

Hepatitis B Virus (HBV) is a DNA-based virus, belonging to the Hepadnaviridae family, which can cause liver disease and increase the risk of developing HCC in infected individuals. Many epidemiological studies have reported that men are more likely to become infected with HBV and to develop HCC(*45*). The gender disparity in HBV-related liver disease has long been recognized and may be attributed to the effects of sex hormones and immune responses (*4*).

Seoung-Ae Lee recently reported a novel HCC-associated W4P/R mutation in the HBV genotype C large surface protein, found exclusively in male HCC patients, which may contribute to sex differences (*46*). HBV integration with androgen receptor-induced TERT upregulation and point mutations in the TERT promoter region have been identified as mechanisms underlying male prevalence in HBV-related HCC (*47*). Androgen may enhance aflatoxin-induced genotoxicity and inflammation, contributing to HCC development in male hepatitis B patients (*47*). The androgen pathway can increase HBV transcription by directly binding to the androgen-responsive element in viral enhancer I (*27*).

The molecular mechanisms of HCC associated with epidemiological risk factors contributing to gender disparity are summarized in Table 3.

5. Gender-biased molecular mechanisms of HCC

Significant differences exist between men and women in DNA damage and repair, X chromosome mutations, and immune system function, which may contribute to disparate incidences and prognosis of HCC. Analysis of these molecular mechanisms may elucidate the

underlying causes of gender disparities in HCC and offer novel insights for future clinical research and therapeutic strategies.

5.1. DNA damage and repair

DNA alterations are fundamental to carcinogenesis, and DNA damage repair (DDR) mechanisms may contribute to gender disparities in cancer incidence. The activation of DNA repair mechanisms following DNA damage is essential for suppressing carcinogenesis. Carcinogenic agents and metabolic processes can induce genetic changes that lead to genomic instability and malignant transformation (*48*). A recent study demonstrated that high DDR activity in HCC is significantly associated with high microsatellite instability (MSI) and high intratumor heterogeneity. Additionally, increased DDR activity correlates with enhanced cell proliferation and poorer survival outcomes in HCC patients (*49*).

DDR alterations in HCC patients have been categorized into two distinct subtypes with heterogeneous clinical and molecular profiles: activated and suppressed DDR. Moreover, DDR status has emerged as a potential biomarker for predicting clinical outcomes in HCC. Typically, men exhibit higher levels of DNA damage, whereas women demonstrate reduced DNA repair capacity (*50*). Following exposure to ionizing radiation, solid tumors occurred more frequently in male survivors of the Hiroshima and Nagasaki atomic bombings (93.7 and 86.9 per 104 person-years, respectively) compared with female survivors (63.7 and 48.8 per 104 person-years, respectively) (*51*). TP53, a key DDR gene, may influence HCC patient survival by modulating anti-tumor immunity (*52*). When exposed to UV-B, male and female vascular smooth muscle cells exhibit sex-specific differences in p53 localization and cell fate, with male cells more prone to apoptosis and female cells more likely to undergo senescence (*53*).

5.2. X chromosome mutation

In mammals, the X chromosome harbors genes that are present in one copy in males (XY) and two copies in females (XX). This dosage difference necessitates complex regulatory mechanisms to ensure proper gene expression, which can influence the severity of diseases caused by X-linked mutations. Tarek Mohamed Kamal Motawi *et al*. identified a promoter SNP (rs2267531) within the glypican-3 gene (GPC3) on the X chromosome, which is associated with HCC in Egyptians (*54*). Sital Singh and colleagues further demonstrated that GPC3 is an X-linked recessive trait, contributing to higher HCC incidence in men compared to women (*55*). Another study revealed that the Wilms tumor gene on the X chromosome is downregulated in HCC tissues, and WTX loss activates the TGF-β pathway, promoting HCC cell proliferation, migration, invasion, and autophagy (*56*). S. H. Yeh showed that X chromosomal

Table 3. The molecular mechanisms of HCC in relation to epidemiological risk factors and gender disparity

Epidemiological risk factors	The molecular mechanisms
Diet	High-fructose diet intake causes increased levels of UDP-GlcNAc and O-GlcNAcylation, and high-cholesterol diet causes increased cholic acid and decreased 3-indolepropionic acid, leading to fatty liver, steatohepatitis, liver fibrosis, and ultimately HCC.
Alcohol and smoking	The mutagenic effect of acetaldehyde toxicity leads to the formation of proteins and DNA adducts. Excessive iron deposition in the liver can cause changes in reactive oxygen species, lipid peroxidation, and metabolism, leading to HCC.
	Smoking causes liver fibrosis, causing DNA damage and oxidative stress. Male smokers have significantly lower T cell and NK cell activities than women, causing HCC.
Metabolic state of the body	Insulin resistance and hyperinsulinemia caused by type 2 diabetes affect the development of HCC through several molecular pathways, including PTEN/P13K/Akt and MAPKK. IR and IGF-1 signaling pathways are the main factors contributing to the development of HCC.
Sex hormones	ERα may inhibit the invasion of HCC cells by transcriptionally regulating the expression of circRNA SMG1.72 by binding directly to the 5' promoter region of its host gene SMG145. PTPRO inhibits JAK and PI3K dephosphorylation-dependent signaling and STAT3 transcriptional activity, thereby suppressing tumorigenesis and development.
	AR by mTORC1 drives hepatic steatosis and HCC development and progression with androgen. AR-V7 enhances c-MYC-driven hepatocellular carcinogenesis by potentiating its oncogenic and diminishing its anti-oncogenic functions. The interaction between TLR4 and AR promotes the development, migration, and invasion of HCC cells.
Hepatitis B virus	A novel HCC-associated W4P/R mutation in HBV genotype C large surface protein, found exclusively in male HCC patients and can cause a sex difference. HBV-integrated AR-induced TERT upregulation and point mutation in TERT promoter region identified as mechanism for male dominance of HBV-related HCC.

allele imbalance contributes to the progression from liver cirrhosis to HCC (*57*). F. Liu *et al*. discovered that the long non-coding RNA FTX (lnc-FTX), an X-inactivation-specific transcript (XIST) regulator, is involved in HCC and may explain gender disparities in disease incidence. lnc-FTX acts as a tumor suppressor by binding to miR-374a and minichromosome maintenance protein 2 (MCM2), potentially contributing to the observed gender differences in HCC (*58*).

5.3. Immune system

The liver is an organ capable of suppressing its immune responses to prevent pathogen invasion and tumor formation. However, immune evasion is a hallmark of inflammation-associated tumorigenesis and can lead to the development of HCC. The HCC tumor microenvironment (TME) is a dynamic system comprising cancer cells, a complex cytokine milieu, the extracellular matrix, immune cell subsets, and other components (*59*). Tumor-associated macrophages (TAMs), neutrophils (TANs), and dendritic cells are key components of the TME and can promote tumor progression, including proliferation, metastasis, and invasion. Immune suppression, particularly of T cells, as observed in chronic liver disease, is associated with the development of HCC (*60*).

Male-dominated sex differences in antitumor immunity are driven by androgen receptor-mediated CD8+ T cell stemness programs. Hyunwoo Kwon *et al*. found that androgens conspire with the CD8+ T cell exhaustion program, contributing to sex bias in cancer (*61*). Additionally, the major circulating estrogens and each of the three estrogen receptors (ERα, ERβ, and G-protein-coupled receptor) regulate the activity of different immune cells, leading to females exhibiting more robust immune responses than males (*62*). Wei *et al*. demonstrated that estrogens can significantly upregulate the NLRP3 inflammasome *via* the E2/ERβ/MAPK pathway, which suppresses the development and progression of HCC (*63*). Moreover, interleukin-6 (IL-6) levels are significantly elevated in HCC patients and correlate with HCC incidence and prognosis (*64*). Naugler *et al*. found that IL-6 levels increase more in males than in females following DEN serum administration (*65*).

5.3.1. Immune cell interactions in the immune microenvironment

The TME of HCC is a complex ecosystem that includes a diverse array of immune cells, such as tumor-associated macrophages (TAMs), regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and natural killer (NK) cells, among others. These immune cells interact with one another and with cancer cells, thereby playing a crucial role in the progression and prognosis of HCC (*60*).

The heterogeneity and dynamic plasticity of TAMs in HCC can influence the progression of the disease by altering their phenotypes in response to changes in the tumor microenvironment. TAMs are categorized into two major subtypes: pro-inflammatory M1 and anti-inflammatory M2 macrophages. M2-type TAMs promote tumor progression and immunosuppression by secreting anti-inflammatory cytokines, such as IL-10 and TGF-β. These cytokines can inhibit the activation and function of T cells and NK cells, thereby suppressing the anti-tumor immune response (*5*). However, the phenotype and function of TAMs differ between cancer patients of different sexes. Multiple studies have demonstrated that men typically exhibit a higher proportion of M2-type TAMs in various tumors, including HCC, a distribution influenced by sex hormones (*6*). This may lead to gender differences in HCC.

Tregs are a subset of T cells with significant immunosuppressive properties that inhibit the proliferation and activation of effector T cells, such as CD8+ T cells, by secreting inhibitory cytokines, including TGF-β and IL-10. This inhibition can weaken the anti-tumor immune response, thereby promoting tumor immune escape and progression (*61*). In HCC, the expression of Tregs exhibits gender differences. Studies have shown that male patients have a higher number of Tregs, and activation of the androgen receptor can enhance the immunosuppressive function of Tregs. This enhancement leads to a weakened anti-tumor immune response, thereby promoting tumor immune escape and progression (*66*). This may be one of the reasons for the poor prognosis of HCC in men.

MDSCs are a group of immature myeloid cells with immunosuppressive functions. They can inhibit the activity of T cells and NK cells by producing reactive oxygen species (ROS) and arginase. In the TME of HCC, MDSCs can suppress the proliferation and activation of T cells and NK cells, resulting in immune tolerance and tumor progression (*67*). Androgens enhance the immunosuppressive function of MDSCs. Research indicates that, within a range of organs, the immune cells primarily consist of myeloid immune cells, such as neutrophils and macrophages, which are positively regulated by androgens (*68*). These findings offer significant insights into the gender differences in HCC.

5.3.2. Molecular immune signaling networks in immune microenvironments

In the TME of HCC, a variety of complex molecular immune signaling networks are involved in modulating the functions of immune cells and their interactions with cancer cells, and these networks exhibit notable gender disparities.

The TGF-β signaling pathway plays a crucial role

in the progression of HCC and exhibits distinct activity patterns between males and females. Male HCC patients often display higher expression levels of TGF-β, which is associated with the promotional effect of androgens on the TGF-β signaling pathway. Androgens can bind to their receptors and enhance the activity of the TGF-β signaling pathway, thereby promoting the epithelial-mesenchymal transition (EMT), invasion, and metastasis of tumor cells, while also suppressing the activity of T cells and natural killer (NK) cells and enhancing the functions of immunosuppressive cells. In contrast, in females, estrogen may inhibit the activity of the TGF-β signaling pathway, reducing its promotion of tumor progression and immunosuppression, thereby helping to maintain anti-tumor immune responses (*65,69*).

The IL-6/STAT3 signaling pathway is a crucial pro-inflammatory pathway that is frequently activated in the TME of HCC. IL-6 can bind to its receptors on immune cells, such as TAMs and Tregs, thereby activating the STAT3 signaling pathway. The activation of STAT3 promotes the production of anti-inflammatory cytokines, such as IL-10 and TGF-β, leading to immune suppression and tumor progression(*64*). Studies have shown that IL-6 levels are significantly higher in male HCC patients, which may be one of the reasons for the faster progression of HCC in males (*70*).

The PI3K/AKT/mTOR signaling pathway is involved in modulating immune cell metabolism and function in the TME of HCC. The activation of this signaling pathway can promote the proliferation and activation of immune cells, such as T lymphocytes and natural killer (NK) cells, and enhance their anti-tumor immune responses. However, the activation of this signaling pathway can also promote the production of immunosuppressive cells, such as TAMs and MDSCs, leading to immune suppression and tumor progression (*71*). Ren QN *et al*. found that the phosphorylation of the androgen receptor by mTORC1 promotes liver steatosis and tumorigenesis, with the PI3K/AKT/mTOR signaling pathway playing a significant role in this process (*25*). This leads to faster progression of HCC tumors in male.

The NLRP3 inflammasome is a multiprotein complex that plays a pivotal role in regulating immune responses within the TME of HCC. The activation of the NLRP3 inflammasome can facilitate the production of pro-inflammatory cytokines, such as IL-1β and IL-18, thereby inducing immune activation and tumor regression (*72,73*). A study conducted by Wei Q *et al*. revealed that estrogens can significantly upregulate the NLRP3 inflammasome *via* the E2/ERβ/MAPK pathway, thereby inhibiting the development and progression of HCC (*63*). Perhaps this is one of the reasons why HCC progresses more slowly in women than in men.

Gender disparity in the molecular mechanisms of HCC in relation with the immune system is summarized in Figure 2.

6. Gene and Epigenetic differences in HCC based on omics analysis

Current multi-omics studies, including genomics,

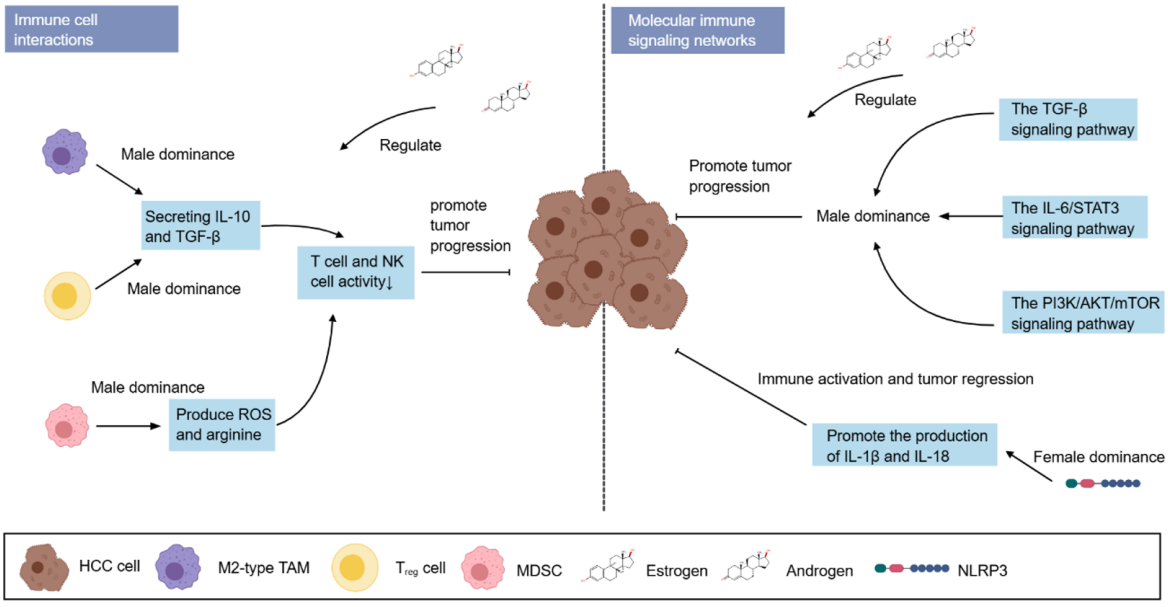

Figure 2. The molecular mechanisms of HCC related with immune system in gender disparity. The left side illustrates the roles of different immune cells in tumor progression. M2-type tumor-associated macrophages (TAMs) and regulatory T cells (Tregs) secrete IL-10 and TGF-β, while myeloid-derived suppressor cells (MDSCs) produce reactive oxygen species (ROS) and arginine. Male-dominant M2-type TAMs, Tregs, and MDSCs can all decrease the activity of T cells and NK cells, thereby promoting tumor progression. The right side shows molecular immune signaling networks. Male-dominant TGF-β, IL-8/STAT3, and PI3K/AKT/mTOR signaling pathways can promote tumor progression. Female-dominant NLRP3 inflammasome can promote the production of IL-1β and IL-18 to activate immune responses and tumor regression.

transcriptomics, proteomics, and metabolomics, have helped us gain a deeper understanding of the mechanisms underlying HCC and its gender differences. These studies have revealed gene mutations, transcriptional regulation, protein expression, and metabolic changes associated with HCC, providing a solid theoretical basis for the development of targeted therapeutic strategies (Figure 3).

6.1. Genomic analysis

Genomics is a cross-disciplinary field that involves the collective characterization, quantitative study, and comparative analysis of genomes across different organisms. It plays a crucial role in the study of HCC. By analyzing the genomes of patients with HCC, scientists can identify specific genetic changes and mutations associated with the pathogenesis and development of HCC. TERT promoter, CTNNB1 and TP53 mutations are the most common alterations identified to date (*74*). A study identified 26 genes that were significantly mutated in HCC. These genes included TP53 (31%), AXIN1 (8%), and RB1 (4%), which were inactivated by mutation, as well as CTNNB1 (27%), an oncogene in the WNT pathway, and the chromatin remodeling genes ARID1A (7%), ARID2 (5%), and BAP1 (5%) (*75*). Another study showed that CTNNB1 was found in only 14% of Taiwanese patients, whereas ALDH2 and KMT2C were mutated at much higher frequencies in this cohort than in TCGA (*76*).

Many studies have found that kras^{V12}, xmrk and Myc oncogenes induce HCC in zebrafish and cause males to develop faster and more severe hepatocellular carcinoma than females (*77*). An examination of HCC patients in Qidong showed that men expressed higher levels of aflatoxin metabolism genes, including AHR and CYP1A1, and lower levels of non-homologous DNA end joining factors, including XRCC4, LIG4 and MRE11, than women, which increased the incidence of HCC (*78*). Bioinformatics analysis showed that compared with female HCC patients, CDK1 and CCNB1 genes were downregulated in males, which is associated with reduced male survival. CYP3A4 and SERPINA4 genes were downregulated in males, which may serve as markers of poor male prognosis (*79*).

6.2. Transcriptomic analysis

Transcriptomics is the study of gene transcription and transcriptional regulation in cells at the whole cell level, and gene expression at the RNA level. A transcriptome

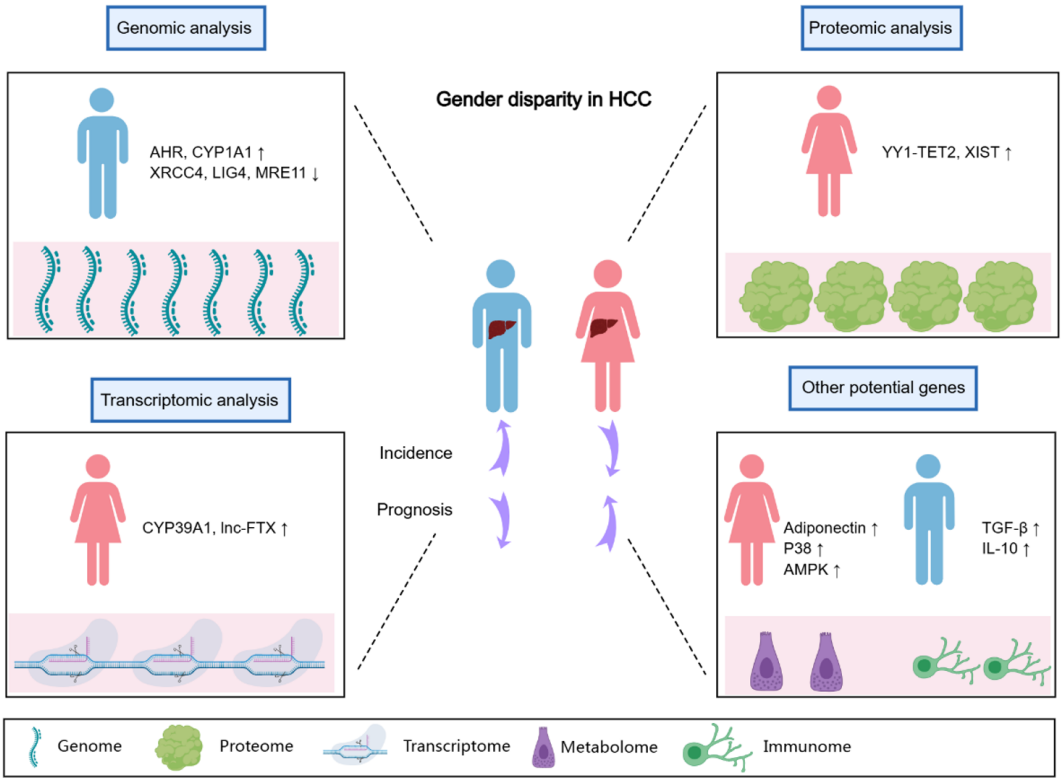

Figure 3. Gene and Epigenetic differences in HCC based on omics analysis. Genome analysis shows that AHR and CYP1A1 gene expression is upregulated in males, while XRCC4, LIG4, and MRE11 gene expression is downregulated. Transcriptome analysis shows that CYP38A1 and lnc-FTX gene expression is upregulated in females. Proteomics analysis shows that the YY1-TET2 protein complex and XIST gene expression are upregulated in females. Metabolomics analysis shows that adiponectin, p38, and AMPK protein expression is upregulated in females. Immunomics analysis shows high expression of TGF-β and IL-10 cytokines in males. The results of these omics analyses explain the gender differences in HCC from different perspectives: males have a higher incidence and worse prognosis.

is the sum of all RNA transcribed by a given tissue or cell at a given stage of development or functional state, including mainly messenger RNA and non-coding RNA. Using single-cell RNA sequencing analysis, Jialu Liang *et al*. identified a cluster of proliferative cancer cells (HCC C4) with significant levels of KI67, TOP2A, and CENPF (*80*). KI-67 expression in HCC is related to differentiation grading, TOP2A is up-regulated in HCC, CENPF is related to the centrosome kinetochore complex and affects cell proliferation and metastasis in HCC (*81*). Complementary to scRNA-seq sequencing, Yue-Fan Wang *et al*. used spatial transcriptome sequencing (ST) analysis to reveal the spatial expression patterns in specific regions of some key molecules, including CCL15, CCL19, and CCL21, which affect the infiltration and recruitment of various immune cells and collectively contribute to the intratumoral heterogeneity of the HCC microenvironment, thereby affecting the prognosis of HCC patients (*82*).

CYP39A1, which is highly expressed in females, blocks the transcriptional activation activity of c-Myc and suppresses the development of HCC through its C-terminal region (*83*). Long non-coding RNA FTX, a regulatory factor highly expressed in females, inhibits HCC proliferation and metastasis. The androgen receptor enhances HBV transcription and replication, which significantly increases the risk of HCC; estrogen suppresses HBV transcription by increasing the hepatic expression of estrogen receptor alpha, which may reduce the risk of HCC (*4*). MiRNA-23a and p53 are activated by estradiol and induce cell apoptosis, conferring a protective role, thereby reducing the risk of HCC in women (*84*). These transcriptomics related studies collectively indicate the reasons for gender differences in HCC, but the specific molecular mechanisms still need further investigation.

6.3. Proteomic analysis

In 1994, Marc Wilkins defined and coined the concept of the proteome. Proteomics, the study of the proteome - how different proteins interact and what role they play in the living organism - provides unique insights into disease biology beyond the genomic and transcriptomic (*85*). Traditionally, HCC has been broadly classified into two major classes based on transcriptomic characteristics, the proliferative class and the non-proliferative class, each comprising ~50% of HCC patients (*86*). Jiang Ying and colleagues classified HCC into subtypes S-I, S-II, and S-III, each of which has a different clinical outcome. The S-III subtype was associated with the lowest overall survival and the highest recurrence rate after first-line surgery and was characterized by proliferation, immune infiltration, and disrupted cholesterol homeostasis (*87*). Based on the proteome molecular classification data of early HCC, Zhiwen Gu *et al*. showed that LYZ levels were significantly increased in the most malignant HCC subgroup (*88*).

Proteomics analysis has also contributed to insights into gender differences in HCC. Zhihui Dai *et al*. found that YY1 and TET2 could interact to form protein complexes that bind to the promoter region of XIST and regulate the methylation level of XIST, and female patients with higher XIST in HCC had a higher overall survival (OS) and longer recurrence-free survival (RFS) (*89*). By high-throughput comparative proteomic analysis, Huiling Li *et al*. identified 1344 differentially expressed proteins (DEPs) in $Hras^{12V}$ transgenic male and female HCC mice, with significantly higher DEPs in males than in females, providing insight into the mechanism of ras oncogene-induced HCC and male-biased HCC (*90*). Another proteomic analysis of Hras12V transgenic mice also showed that 5 pathways in males but only 1 in females were significantly altered in terms of up-regulated proteins in tumor tissues compared with normal liver tissues (*91*). These data indicate that female hepatocytes are more difficult to be disturbed by oncogenes.

6.4. Other potential genes

Besides genomics, proteomics and transcriptomics, omics also includes metabolomics, immunomics, *etc*., which are related and together explain the gender differences of HCC.

Cancer cells have metabolic dysregulation to support the demands of uncontrolled proliferation. Metabolomics is the global analysis of small-molecule metabolites, providing critical information about how cancer and cancer treatment interact with metabolism at the cellular and systemic level (*92*). Non-targeted metabolomics and stable isotope tracing revealed that high levels of dietary fructose promote the progression of HCC through the enhancement of O-GlcNAcylation *via* microbiota-derived acetate (*41*). Loss of the metabolic regulator Sirt5 leads to abnormal bile acid levels and the immunosuppressive microenvironment favoring the development of HCC (*93*). The decrease in propionyl-CoA metabolism mediated by ALDH6A1 contributes to metabolic remodeling and facilitates hepatocarcinogenesis (*94*). Specific diacylglycerols enriched by hepatic lipogenesis increase the transcriptional activity of hepatic AR and increase the risk of HCC, a novel mechanism underlying the higher risk of HCC in obese/NAFLD men (*95*). Adiponectin is a hormone secreted by fat cells, with higher levels in women. It can inhibit HCC proliferation and damage its growth through activation of p38 and AMPK proteins in liver cells (*96*). Research has shown that although women's fasting triacylglycerol levels are higher, they can more effectively take advantage of the protective effects of N^6-methyladenosine (m6A) modification and achieve greater health benefits under a high-fat diet, explaining the sex differences in liver metabolism from

the perspective of RNA modification (*97*).

Immunomics technology has also provided a new perspective for studying gender differences in HCC. By analyzing the composition of immune cells, immune signaling pathways, and the regulatory effects of sex hormones on immune responses, studies have revealed significant differences between genders in the occurrence, progression, and immune treatment responses of HCC. For example, activation of the androgen receptor can modulate the function of immune cells and affect the expansion of regulatory T cells, thereby inhibiting antitumor immune responses (*98*). In addition, targeting the androgen receptor signaling pathway can enhance the efficacy of immunotherapy, offering new strategies for personalized treatment of HCC. Males have a higher proportion of M2 (anti-inflammatory) macrophages. M2-type tumor-associated macrophages (TAMs) promote tumor progression and immune suppression by secreting anti-inflammatory cytokines (such as IL - 10 and TGF - β), resulting in a worse prognosis for male HCC (*99*). These findings indicate that immunomics plays a significant role in elucidating the underlying mechanisms of gender differences in HCC.

The detailed gene and epigenetic differences in HCC based on omics analysis are summarized in Table 4.

7. Conclusions and perspectives

HCC exhibits striking gender disparities in incidence and prognosis, with males generally experiencing higher rates of occurrence and worse outcomes compared to females. These disparities are shaped by a complex interplay of epidemiological, molecular, and genetic factors. While traditional risk factors such as hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol consumption, and metabolic syndrome contribute to these differences, recent advances in molecular biology and multi-omics analysis have provided deeper insights into the underlying mechanisms.

Sex hormones, such as estrogen and androgen, play pivotal roles in modulating HCC progression. Estrogen receptor (ER) signaling is generally protective, suppressing tumor development, while androgen receptor (AR) signaling promotes tumorigenesis. Additionally, gender-specific differences in DNA damage repair, immune microenvironments, and genetic/epigenetic factors further contribute to the observed disparities. For instance, males typically exhibit higher levels of immunosuppressive cells such as M2-type tumor-associated macrophages (TAMs) and regulatory T cells (Tregs), which dampen anti-tumor immune responses. Multi-omics analyses, including genomics, transcriptomics, and proteomics, have revealed sex-specific differences in gene expression, protein interactions, and metabolic pathways, providing a foundation for developing targeted therapeutic strategies.

Despite these advances, significant gaps remain in understanding the precise mechanisms driving gender disparities in HCC. Future research should prioritize the following directions:

i) Identification of Novel Molecular Targets: Further exploration of gender-specific molecular pathways, particularly those involving sex hormones, immune microenvironments, and epigenetic modifications, is critical. For example, elucidating how estrogen and androgen signaling interact with metabolic pathways and

Table 4. The detailed gene and epigenetic differences in HCC based on omics analysis

Category	Name	Gender Differences
Genes	*krasV12, xmrk, Myc*	Induces faster and more severe HCC in males compared to females.
	AHR, CYP1A1	Higher expression in males, associated with increased HCC incidence.
	XRCC4, LIG4, MRE11	Lower expression in males, associated with increased HCC incidence.
	CDK1, CCNB1	Downregulated in males, associated with reduced male survival.
	CYP3A4, SERPINA4	Downregulated in males, may serve as a marker of poor male prognosis.
	CYP39A1	Highly expressed in females, inhibits HCC development by blocking c-Myc activity.
	lnc-FTX	Highly expressed in females, inhibits HCC proliferation and metastasis.
	AR	Enhances HBV transcription and replication, increasing HCC risk, more impactful in males.
	ERα	Suppresses HBV transcription in females, reducing HCC risk.
	XIST	Higher expression in female HCC patients, associated with better overall survival and recurrence-free survival.
	ALDH6A1	Mediates decreased propionyl-CoA metabolism in males, facilitating hepatocarcinogenesis.
Proteins	YY1	Forms complexes with TET2 to regulate XIST methylation, influencing survival in female HCC patients.
	TET2	Forms complexes with YY1 to regulate XIST methylation, influencing survival in female HCC patients.
	p38, AMPK	Activated by adiponectin in females, inhibits HCC proliferation.
Metabolites	Propionyl-CoA	Decreased metabolism in males, promoting hepatocarcinogenesis.
	Specific diacylglycerols	Increased in obese/NAFLD males, activates AR and increases HCC risk.
Other Molecules	m6A modification	More effectively utilized by females for protection under high-fat diets, explaining sex differences in liver metabolism.
	Adiponectin	Higher levels in females, inhibits HCC proliferation through activation of p38 and AMPK.
Cytokines	IL – 10, TGF - β	Higher expression in males, associated with increased HCC incidence.

immune cells could reveal new therapeutic targets.

ii) Integration of Multi-Omics Data: Combining genomics, transcriptomics, proteomics, and metabolomics data will help uncover the complex interplay between genetic, epigenetic, and environmental factors in shaping gender disparities. This integrative approach may identify biomarkers for early diagnosis and personalized treatment.

iii) Development of Gender-Specific Therapies: Given the distinct molecular and immunological profiles between males and females, therapeutic strategies tailored to gender-specific mechanisms should be explored. For instance, estrogen-related drugs or AR-targeted therapies may offer promising avenues for improving outcomes in HCC patients.

iv) Longitudinal and Population-Based Studies: Large-scale, longitudinal studies are needed to better understand how gender differences in HCC evolve over time and across diverse populations. These studies should account for regional, ethnic, and socioeconomic variations in risk factors and outcomes.

v) Prevention and Public Health Interventions: Targeted public health initiatives aimed at reducing gender-specific risk factors, such as alcohol consumption, smoking, and metabolic syndrome, could help mitigate gender disparities in HCC incidence and prognosis.

In conclusion, addressing the challenges of gender disparities in HCC requires a multidisciplinary approach that integrates epidemiological, molecular, and clinical insights. By prioritizing research into the underlying mechanisms and translating these findings into clinical practice, we can improve diagnostic, prognostic, and therapeutic outcomes for both male and female patients. Future studies should continue to explore the interactions between environmental, hormonal, and genetic factors to develop personalized therapeutic strategies for HCC in different sexes.

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