

Review

Metabolic Dysfunction-Associated Steatotic Liver Disease and Extrahepatic Cancers

Shiyu Peng¹, Zhui Ke², Han Ding³, Xinyu Wang³, Huiling Cao³, Yuzhu Song³, Yingying Nie⁴, Yang Zhao⁵, Jianni Qi^{6,*}, Qiang Zhu^{1,3,6,*}

¹Department of Gastroenterology, The First Affiliated Hospital of Xinjiang Medical University, 830054 Urumqi, Xinjiang, China

²Department of Oncology, Shanghai Tenth People's Hospital, School of Medicine, Tongji University, 200072 Shanghai, China

³Department of Gastroenterology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, 250021 Jinan, Shandong, China

⁴School of Medicine, Shihezi University, 832000 Shihezi, Xinjiang, China

⁵Department of Oncology, The First Affiliated Hospital of Jinan University, 510630 Guangzhou, Guangdong, China

⁶Department of Central Laboratory, Shandong Provincial Hospital Affiliated to Shandong First Medical University, 250021 Jinan, Shandong, China

*Correspondence: slqijn@126.com (Jianni Qi); zhuqiang@sdu.edu.cn (Qiang Zhu)

†These authors contributed equally.

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease globally, and its high prevalence underscores the central role of metabolic dysregulation in its pathogenesis. Recent epidemiological studies have shown that MASLD is associated not only with hepatocellular carcinoma but also with an increased risk of several extrahepatic malignancies, including esophageal, gastric, colorectal, pancreatic, thyroid, breast, endometrial, renal, and prostate cancers. This review summarizes the emerging epidemiological links between MASLD and these extrahepatic cancers and discusses the biological mechanisms that may underlie these associations. We aim to describe both shared and organ-specific pathogenic pathways, highlight the importance of viewing MASLD as a systemic metabolic disorder in cancer prevention and clinical management, and outline future research directions from both conceptual and clinical perspectives. Future efforts should focus on biomarker development, multidisciplinary collaboration, and interventions targeting metabolic pathways.

Keywords: metabolic dysfunction-associated steatotic liver disease; tumor microenvironment; insulin resistance; extrahepatic cancer

1. Introduction

The prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) has increased substantially, with a global prevalence of 38.77% [1]. The disease burden is particularly high in Asia, Latin America, the Middle East, and North Africa, where the prevalence rates exceed 40% in certain regions [2,3]. Therefore, MASLD has become an important global public health concern and is increasingly recognised as a hepatic manifestation of a complex multi-system metabolic disease rather than an isolated liver disorder. Beyond its progression to liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC), growing evidence indicates that MASLD is associated with an increased risk of several extrahepatic malignancies. This association is supported by large-scale cohort studies and meta-analyses. For example, a study based on extensive datasets, including the UK Biobank, showed that MASLD was associated with an increased risk of 24 site-specific cancers, with the strongest associations observed in liver, thyroid, pancreatic, gastric, and colorectal cancers (CRC) [4]. Another study reported significantly higher incidences of thyroid, breast, colorectal, and pancreatic cancers, along with increased cancer-related mortality among individuals with MASLD than among those without [5]. Collectively,

these findings underscore the importance of MASLD prevention and management in reducing cancer risk.

1.1 The Core Role of Metabolic Disorders and Chronic Inflammation

The development and progression of MASLD are closely associated with chronic inflammation at both hepatic and systemic levels. Insulin resistance (IR), a major driver of MASLD, promotes hepatic lipid accumulation and subsequent lipotoxicity. Lipotoxicity induces oxidative stress and endoplasmic reticulum stress in hepatocytes, which in turn activates inflammatory signalling pathways, including nuclear factor kappa B (NF-κB) and c-Jun N-terminal kinase (JNK). These events stimulate the release of pro-inflammatory cytokines, such as tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), from Kupffer cells and other cellular sources, thereby promoting persistent hepatic inflammation [6,7]. This chronic inflammatory state further aggravates IR in both hepatic and peripheral tissues, creating a vicious cycle that contributes to the transition from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH) [8,9]. Therefore, targeting this inflammatory circuit may be an important therapeutic strategy to limit MASLD progression.



1.2 Alterations in the Immune Microenvironment

MASLD progression is closely associated with the dysregulation of the hepatic immune microenvironment. Lipotoxicity and metabolic stress in MASLD promote the recruitment and activation of diverse immune cell populations. Hepatic macrophages shift toward a pro-inflammatory M1-like phenotype, while CD8⁺ cytotoxic T cells and neutrophils accumulate in the liver, collectively driving chronic inflammation and disrupting immune homeostasis. These immune alterations are thought to contribute to the transition from simple steatosis to MASH and liver fibrosis [10]. Simultaneously, the hepatic cytokine milieu is markedly altered. Pro-inflammatory cytokines, including TNF- α , IL-6, and IL-1 β , released by activated immune cells, aggravate local IR and hepatocyte injury and may activate pro-oncogenic signalling pathways that promote hepatocarcinogenesis. In addition, dysregulated IL-22 signalling, given its dual regenerative and pro-tumourigenic effects, may further increase the risk of liver cancer in MASLD [11].

The systemic and local immunosuppressive states associated with MASLD may promote the development of extrahepatic tumours. The liver is a key immune organ involved in systemic immune surveillance, and its dysfunction may impair this protective role. Moreover, the hepatic accumulation of immunosuppressive cell populations, including myeloid-derived suppressor cells and regulatory T cells, contributes to an immune-tolerant microenvironment that allows extrahepatic tumour cells to escape immune surveillance [12]. In this context, MASLD may shift the liver from an immune surveillance organ toward a more immune-permissive state. Disruption of the hepatic immune microenvironment, together with broader systemic effects, may therefore contribute to an increased risk of extrahepatic cancers. In this review, we summarise the epidemiological evidence linking MASLD to major extrahepatic cancers, including colorectal, thyroid, breast, pancreatic, renal, endometrial, gastric, and oesophageal cancers (Fig. 1). The molecular mechanisms that may underlie these associations are also discussed (Table 1). We hope that this review will inform future research and clinical management in this field.

2. Associations Between MASLD and Extrahepatic Cancers

2.1 MASLD and Oesophageal Cancer

Multiple large-scale cohort studies have shown a significantly increased incidence of oesophageal cancer in patients with MASLD. A retrospective cohort study involving over 8.12 million adults from the Korean National Health Insurance Service (NHIS) database found that individuals with MASLD, defined by a Fatty Liver Index (FLI) ≥ 60 , had a markedly higher risk of developing oesophageal cancer compared to the non-MASLD population (hazard ratio (HR) = 2.10, 95% confidence interval (CI): 1.88–2.35) [13].

This study, which included an adult population, also indicated that MASLD contributes to an elevated risk of digestive tract cancer in younger adults, revealing a clear, albeit non-significant, trend toward an increased risk in individuals aged 20–39 (adjusted HR 1.67) [14]. Additionally, a large Chinese cohort study reported a significantly heightened risk of oesophageal cancer in patients with MASLD (HR = 4.37, 95% CI: 2.55–7.49), with the risk positively correlating with the severity of co-existing metabolic abnormalities [15]. The relationship between MASLD and the two predominant histological subtypes of oesophageal cancer, oesophageal squamous cell carcinoma (ESCC) and oesophageal adenocarcinoma (EAC), appears to be distinct. ESCC is primarily associated with factors such as smoking, alcohol consumption, and nutritional deficiencies, while EAC is more closely linked to obesity, gastroesophageal reflux disease (GERD), and metabolic syndrome [16,17]. A study indicated a strong correlation between MASLD and EAC, potentially mediated by chronic inflammation, dysregulated lipid metabolism, and signalling along the liver-gastroesophageal axis [18]. These epidemiological findings robustly suggest that fatty liver disease is a marker of hepatic pathology as well as a significant risk factor for gastrointestinal malignancies, including oesophageal cancer. This underscores the need for improved early screening and risk management in patients with MASLD. Overall, MASLD serves as a crucial epidemiological marker for oesophageal cancer, particularly EAC, highlighting the importance of its identification and clinical management.

Systemic chronic inflammation induced by MASLD is a critical mechanism that promotes DNA damage and the accumulation of mutations in oesophageal mucosal cells. In the context of obesity and fatty liver, adipocyte hypertrophy and hyperplasia result in the increased secretion of various pro-inflammatory cytokines, including IL-1, IL-6, IL-8, and TNF- α . This process is accompanied by elevated levels of C-reactive protein (CRP), free fatty acids, and reactive oxygen species (ROS), which create a chronic low-grade inflammatory environment [19,20]. Subsequently, the NF- κ B signalling pathway is activated, promoting the expression of inflammatory mediators, exacerbating the inflammatory response in the oesophageal mucosa, and inducing DNA damage and genetic mutations, thereby facilitating tumorigenesis [21,22]. Oxidative stress appears to have context-dependent effects in oesophageal cancer. Li et al. [23] showed that TFRC expression was increased under oxidative and endoplasmic reticulum stress and that TFRC promoted oesophageal cancer cell proliferation, migration and invasion through the HIF-1 α and NOTCH1 signalling pathways. In contrast, excessive mitochondrial oxidative stress induced by sulconazole promoted PANoptosis and inhibited glycolysis, thereby suppressing oesophageal cancer cell proliferation and migration and enhancing radiosensitivity [24]. These findings suggest that the biological effects of oxidative stress in oesophageal cancer depend on its magnitude and cellular context. Oxidative

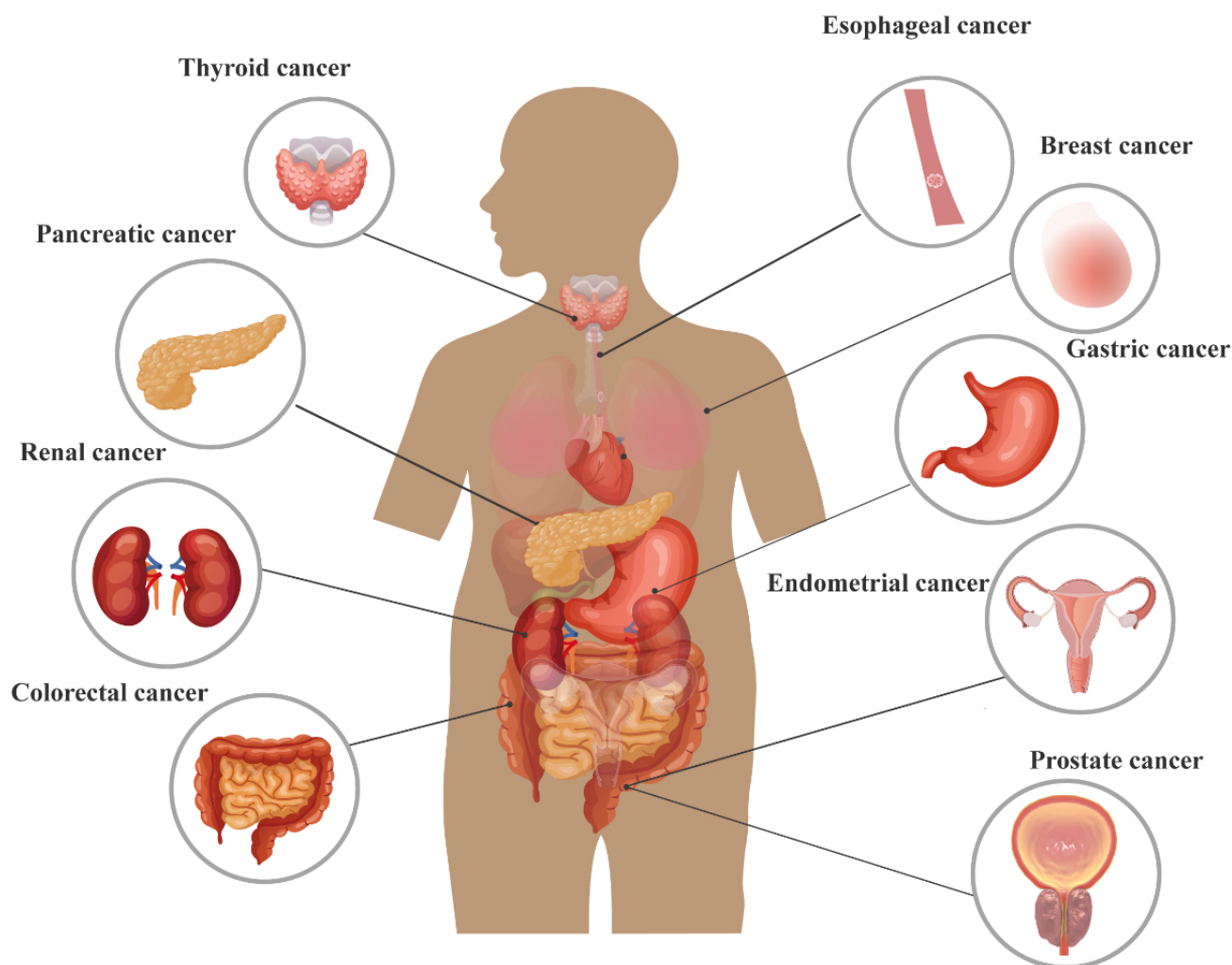


Fig. 1. MASLD-associated cancers: a spectrum of common extrahepatic malignancies. The figure was prepared using Adobe Illustrator 2025 (Adobe Inc., San Jose, CA, USA). MASLD, metabolic dysfunction-associated steatotic liver disease.

stress and endoplasmic reticulum (ER) stress have been implicated in the progression of oesophageal cancer. In particular, TFRC expression is increased under oxidative and ER stress conditions and has been shown to promote oesophageal cancer cell proliferation, migration and invasion through the HIF-1 α and NOTCH1 signalling pathways [23]. Chronic inflammation may also induce pyroptosis in inflammatory cells, releasing numerous pro-inflammatory mediators that facilitate the progression of oesophageal cancer [25,26]. Furthermore, the chronic inflammatory state associated with fatty liver exacerbates oesophageal carcinogenesis by modulating gut dysbiosis [27].

Mendelian randomisation studies have demonstrated a strong association between IR indices, such as the triglyceride-glucose (TyG) index and the metabolic score for IR (METS-IR), and the risk of oesophageal cancer, particularly highlighting a significant increase in the risk of EAC [28]. The abnormal accumulation of fatty acid metabolites in patients with MASLD underpins the altered energy metabolism observed in tumours. The synthesis and degradation of fatty acids are essential for regulating

energy supply and constructing membrane lipids in cancer cells, thereby influencing their migratory and invasive properties [29,30]. For example, activation of sterol regulatory element-binding transcription factor 1 (SREBF1), a critical enzyme in fatty acid synthesis, facilitates the reprogramming of fatty acid metabolism, which in turn enhances the proliferation and metastasis of oesophageal cancer cells [31]. Additionally, increased fatty acid β -oxidation generates ATP for tumour cells, thereby supporting their survival and contributing to drug resistance [32]. Furthermore, lipid metabolism-associated proteins, such as Opa interacting protein 5 (OIP5), regulate the expression of acyl-CoA synthetase long-chain family member 1 (ACSL1), thereby influencing fatty acid metabolism in ESCC and promoting tumour progression [33]. Metabolic abnormalities further advance the development of oesophageal cancer by modulating the function of immune cells within the TME [34].

2.2 MASLD and Gastric Cancer

Substantial clinical and epidemiological studies have established a strong association between MASLD and the

Table 1. The key mechanisms by which MASLD promotes extratumoral tumorigenesis.

Cancer type	Mechanisms	Key signaling pathways
Esophageal Cancer	Hyperinsulinemia, Tumor Microenvironment	HIF-1 α , NOTCH1, NF- κ B
Gastric Cancer	Hyperinsulinemia, Systemic Inflammation	/
Colorectal Cancer	Gut Dysbiosis, Impaired Intestinal Barrier, Metabolic Endotoxemia, Fatty Acid Accumulation	NF- κ B, Wnt/ β -catenin
Pancreatic Cancer	Hyperinsulinemia, Pancreatic Fat Infiltration and Local Inflammation	PI3K/Akt, MAPK, NF- κ B
Thyroid Cancer	Hyperinsulinemia, IGF-1 Axis Activation, Adipokine Imbalance	PI3K/Akt, MAPK, JAK/STAT
Breast Cancer	Enhanced Adipose Tissue Aromatization (Elevating Estrogen Levels), Systemic Inflammation, Immune Microenvironment Remodeling	ER Signaling, JAK/STAT, PI3K/Akt
Endometrial Cancer	Hyperinsulinemia, Inflammation and Immune Microenvironment Remodeling, Hormone Metabolism	PI3K-AKT-mTOR, NF- κ B, HIF, PPAR γ
Renal Cancer	Abnormal Lipid Metabolism and Lipotoxicity, Metabolic Reprogramming, Synergistic Interaction with the HIF Pathway	NF- κ B/STAT3
Prostate Cancer	Fatty Acid Metabolic Reprogramming, Chronic Inflammation–Immune Microenvironment Remodeling	NF- κ B, STAT3, AR signaling

Abbreviations: MASLD, metabolic dysfunction-associated steatotic liver disease; HIF-1 α , hypoxia-inducible factor-1 alpha; NOTCH1, notch receptor 1; NF- κ B, nuclear factor kappa B; PI3K/Akt, Wnt/ β -catenin, phosphoinositide 3-kinase/protein kinase B; MAPK, mitogen-activated protein kinase; JAK/STAT, Janus kinase/signal transducer and activator of transcription; PI3K-AKT-mTOR, phosphoinositide 3-kinase/protein kinase B/mechanistic target of rapamycin; PPAR γ , peroxisome proliferator-activated receptor gamma; STAT3, signal transducer and activator of transcription 3; AR, androgen receptor; IGF-1, insulin-like growth factor-1.

incidence and prognosis of gastric cancer. A nationwide cohort study utilising the Korean National Health Insurance Service database, which encompassed over 8 million examinees, revealed that patients with MASLD (FLI ≥ 60) faced a significantly heightened risk of developing gastric cancer (HR = 1.18, 95% CI: 1.14–1.22) and experienced increased all-cause mortality related to gastric cancer [13]. The risk of gastric cancer was also elevated among young adults (aged 20–39) with MASLD, indicating that fatty liver may serve as an important independent risk factor for gastric cancer in this demographic [14]. Additionally, another Asian multicentre retrospective cohort study found that while patients with biopsy-confirmed MASLD had lower liver cancer-related mortality, they demonstrated a higher incidence of non-hepatic malignancies, including gastric cancer, suggesting a potential role of MASLD in promoting gastric carcinogenesis [35]. However, studies have reported a slightly lower incidence of gastric cancer in patients with MASLD than in the general population, which may be attributed to variations in study populations, diagnostic criteria, and comorbid conditions [36].

The prognosis of gastric cancer in patients with MASLD is often complicated by the presence of metabolic disorders such as obesity and diabetes, which can hinder treatment and increase the risk of complications [13,35]. Additionally, patients with concurrent MASLD and gastric cancer frequently exhibit multiple metabolic disturbances, necessitating a thorough evaluation of liver function, metabolic status, and tumour stage during treatment. This complexity presents significant challenges for clinical management [13,35]. Overall, the clinical epidemiological data indicate that MASLD serves as an independent risk factor for gastric cancer, underscoring the need for im-

proved screening and monitoring of gastric cancer in such patients.

The systemic inflammatory state induced by MASLD significantly affects the gastric mucosa. Patients with fatty liver experience chronic low-grade inflammation, characterised by elevated levels of pro-inflammatory cytokines (e.g., IL-1, IL-6, TNF- α) and chemokines (e.g., C-X-C motif chemokine ligand 1 (CXCL1)). These factors trigger hepatic inflammation and may modulate the inflammatory response in the gastric mucosa via the circulatory system, thereby promoting abnormal hyperplasia and malignant transformation of gastric mucosal cells [19,37]. Furthermore, metabolic disturbances associated with MASLD result in IR and hyperinsulinemia. This condition fosters the proliferation and anti-apoptotic activity of gastric cancer cells through the insulin and insulin-like growth factor-1 (IGF-1) signalling pathways, consequently enhancing tumour growth capacity. Additionally, the oxidative stress induced by MASLD serves as a significant contributor to DNA damage and gene mutations in gastric cells. Elevated ROS levels in the liver of patients with MASLD lead to lipid peroxidation and DNA damage; this oxidative stress can systematically impact gastric cells through circulation, inducing genetic mutations and tumorigenesis [35,38]. Notably, the aberrant expression of specific enzymes (e.g., aldo-keto reductase family 1 member B10 (AKR1B10)) in patients with MASLD has also been associated with cytoprotective mechanisms and chemotherapy resistance during the development of gastric cancer [39]. In summary, MASLD facilitates the initiation and progression of gastric cancer through a synergistic interplay of induced systemic inflammation, metabolic disturbances, and oxidative stress.

2.3 MASLD and CRC

Recently, numerous high-quality meta-analyses and large-scale cohort studies have consistently demonstrated that patients with MASLD have a significantly increased risk of developing CRC and its precursor lesion, colorectal adenoma [40]. A meta-analysis encompassing over 9 million participants revealed that the summary HR for CRC was 1.42 (95% CI: 1.29–1.56), while the HR for colorectal adenoma was even greater 1.51 (95% CI: 1.31–1.74) [41]. Importantly, this risk is closely correlated with the severity of MASLD. Patients exhibiting advanced liver fibrosis (stage F3–F4) have a more than 2.5-fold increased risk of CRC compared to those with simple steatosis, underscoring the role of liver pathological progression as a significant factor in colorectal carcinogenesis [42]. Moreover, the association between MASLD and CRC is particularly pronounced in Asian populations, suggesting that genetic background and environmental factors may serve as effect modifiers.

Patients with MASLD frequently exhibit profound disturbances in the gut–liver axis, which is characterised by intestinal dysbiosis and hepatic metabolic dysfunction, further reshaping the intestinal microenvironment. In addition, MASLD is associated with reduced microbial diversity, depletion of beneficial short-chain fatty acid (SCFA)-producing bacteria, such as *Faecalibacterium prausnitzii* and *Roseburia* spp., and enrichment of Gram-negative, lipopolysaccharide (LPS)-producing pathobionts, including *Fusobacterium nucleatum* and *Escherichia coli*. SCFAs, especially butyrate, are essential for maintaining colonic epithelial energy supply, epithelial integrity, and mucosal immune homeostasis, partly through inhibition of histone deacetylases. Therefore, the depletion of SCFA-producing bacteria compromises gut barrier function and weakens local anti-inflammatory defences. In parallel, *F. nucleatum* may directly promote colorectal carcinogenesis through its FadA adhesin, which binds to E-cadherin on intestinal epithelial cells, activates β -catenin signalling, and enhances local inflammatory responses [43,44]. Notably, MASLD-related hepatic metabolic abnormalities further aggravate intestinal dysfunction. Hepatic steatosis and IR alter bile acid synthesis and composition, thereby disturbing farnesoid X receptor (FXR) and Takeda G protein-coupled receptor 5 (TGR5) signalling in the intestine, which are critical for maintaining epithelial barrier integrity, microbial homeostasis, and mucosal immunity. Furthermore, the steatotic liver releases a variety of hepatokines, inflammatory mediators, and metabolic signals that may further influence intestinal epithelial cells and the gut microbial ecosystem, thereby reinforcing gut barrier disruption. Consequently, tight junction proteins such as occludin and zonula occludens-1 (ZO-1) are downregulated, intestinal permeability increases, resulting in a “leaky gut” phenotype.

This impaired intestinal barrier facilitates the translocation of bacterial products, particularly LPS, into portal circulation, leading to metabolic endotoxemia. LPS subsequently binds to Toll-like receptor 4 (TLR4) on hepatocytes, Kupffer cells, and possibly extrahepatic immune cells, triggering the myeloid differentiation primary response 88 (MyD88)-dependent pathway and activating NF- κ B and inflammasome signalling. This cascade induces persistent production of pro-inflammatory cytokines, including TNF- α , IL-6, and IL-1 β , thereby sustaining systemic chronic inflammation [45]. Collectively, these alterations establish a protumorigenic microenvironment that promotes colorectal epithelial proliferation, immune dysregulation, and malignant transformation.

Excess free fatty acids (FFAs) derived from the MASLD liver and adipose tissue, in conjunction with circulating pro-inflammatory cytokines, create a pro-carcinogenic metabolic-inflammatory environment. In colorectal epithelial cells, FFAs and cytokines, such as TNF- α and IL-6, can synergistically activate the NF- κ B pathway. Once activated, NF- κ B translocates to the nucleus, leading to the upregulation of genes associated with cell proliferation (e.g., Cyclin D1), anti-apoptosis (e.g., Bcl-2, Bcl-xL), angiogenesis (e.g., vascular endothelial growth factor (VEGF)), and metastasis. Notably, the inflammatory environment associated with MASLD is closely linked to the aberrant activation of the Wnt/ β -catenin signalling pathway, a critical event in approximately 80% of CRC cases. Inflammatory cytokines can destabilise the “ β -catenin destruction complex”, which comprises the adenomatous polyposis coli (APC) protein, axin, and glycogen synthase kinase-3 β (GSK-3 β). This destabilisation results in the accumulation of β -catenin in the cytoplasm and its subsequent translocation to the nucleus, where it interacts with T-cell factor/Lymphoid enhancer factor (TCF/LEF) transcription factors. This interaction initiates the transcription of proto-oncogenes such as c-Myc and Cyclin D1, thereby driving the abnormal proliferation and self-renewal of intestinal stem/progenitor cells and ultimately initiating and promoting the adenoma-carcinoma sequence [46,47].

2.4 MASLD and Pancreatic Cancer

Recent research has increasingly focused on the relationship between MASLD and the onset of pancreatic cancer. Clinical data have revealed that patients with MASLD face a markedly higher risk of developing pancreatic cancer, especially those with concurrent metabolic syndromes such as diabetes. Systematic reviews and meta-analyses have indicated that individuals with MASLD have a 32% higher risk of pancreatic cancer than those without MASLD [48]. Additional potential mechanisms include the accumulation of endogenous fatty acids, which may lead to pancreatic cell apoptosis and tumorigenesis [49]. Numerous clinical studies and extensive cohort analyses have substantiated the association between MASLD and pancreatic can-

cer. Research utilising the UK Biobank revealed a significant correlation between MASLD and the incidence of various cancers, including pancreatic cancer. This investigation, analysing 352,911 participants, demonstrated a notably higher incidence of pancreatic cancer among patients with MASLD compared to those without, yielding an HR of 1.31 (95% CI 1.10–1.56) [50]. Furthermore, a systematic review and meta-analysis integrating multiple studies consistently identified an association between MASLD and pancreatic cancer across diverse geographical regions and study methodologies [48]. Clinical observations suggest that patients with pancreatic cancer with concurrent MASLD frequently experience poorer overall survival and recurrence-free survival rates following surgical resection. This indicates that MASLD may affect the biological behaviour of pancreatic cancer, potentially rendering it more aggressive or treatment-resistant.

MASLD-associated hyperinsulinaemia is pivotal in the pathogenesis of pancreatic cancer [18]. Pancreatic ductal epithelial cells exhibit high expression of IR and IGF-1 receptors (IGF-1R). Elevated concentrations of insulin and IGF-1 activate these receptors and their downstream signalling pathways, including phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) and mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), which directly stimulate ductal cell proliferation and promote resistance to apoptosis. Prolonged Akt activation further enhances protein and lipid synthesis through the mechanistic target of rapamycin (mTOR) pathway, thereby fulfilling the bioenergetic requirements of rapidly proliferating cancer cells [51,52,53]. Moreover, IR and hyperglycaemia can lead to excessive ROS production, resulting in oxidative DNA damage and genomic instability. This process heightens the likelihood of mutations in driver genes, such as the KRAS proto-oncogene, GTPase (KRAS), which serves as the initiating event in the majority of pancreatic cancer cases [54,55,56]. MASLD frequently coexists with nonalcoholic fatty pancreatic disease (NAFPD), and their association may reflect a coordinated, multiorgan manifestation of metabolic dysfunction. Rather than acting independently, MASLD and NAFPD may exert mutually reinforcing effects in pancreatic carcinogenesis. MASLD is characterised by systemic insulin resistance, lipotoxicity, and chronic low-grade inflammation, which promote ectopic fat deposition in the pancreas through increased levels of circulating free fatty acids, inflammatory cytokines, and hepatokines. Thus, MASLD may contribute to the initiation and progression of NAFPD by creating a metabolic environment favourable for pancreatic steatosis and injury, which in turn leads to fat infiltration within the pancreas, further amplifying local inflammation and fibrogenesis. Adipocytes in the pancreatic parenchyma secrete adipokines and pro-inflammatory mediators, while lipid overload induces oxidative stress and cellular injury. These changes activate pancreatic stellate cells, which secrete extracellular matrix components, cy-

tokines, and growth factors, thereby driving fibrosis and forming the characteristic desmoplastic stroma of pancreatic cancer. Importantly, this local fibro-inflammatory response may be enhanced by the systemic inflammatory signals associated with MASLD. Through reciprocal interactions among adipocytes, pancreatic stellate cells, immune cells, and tumour cells, MASLD and NAFPD may establish a vicious cycle that promotes tumour growth, invasion, immune evasion, and therapeutic resistance [57,58,59].

2.5 MASLD and Thyroid Cancer

Multiple cohort studies involving diverse populations have consistently demonstrated that MASLD, particularly when closely linked to central obesity and metabolic syndrome, is an independent risk factor for papillary thyroid cancer. A large-scale prospective cohort study, following multivariable adjustment, revealed that patients with MASLD exhibited an HR of 1.36 (95% CI: 1.12–1.65) for the development of thyroid cancer [60]. This study revealed a significantly elevated risk of lymph node metastasis in patients with MASLD (odds ratio (OR) = 1.285, 95% CI: 1.052–1.570), as well as a higher likelihood of the BRAF V600E mutation and more advanced tumour stages. These associations were particularly pronounced in patients who were also diagnosed with Hashimoto's thyroiditis, hypertension, diabetes, hypertriglyceridaemia, low high-density lipoprotein cholesterol, and obesity. The influence of MASLD on lymph node metastasis, the B-Raf proto-oncogene, serine/threonine kinase, and V600E mutation (BRAF V600E mutation) is especially significant in female patients [61].

IR, the core pathophysiological feature of MASLD, results in compensatory hyperinsulinaemia, which serves as an “initiating factor” in thyroid carcinogenesis. Thyroid follicular epithelial cells exhibit high expression of both IR and IGF-1R. Elevated insulin concentrations can produce IGF-1-like mitogenic effects either through “hybrid receptors” or by directly binding to IGF-1R. The binding of insulin and IGF-1 to their respective receptors activates receptor tyrosine kinase autophosphorylation, which subsequently recruits and activates the downstream adaptor protein insulin receptor substrate 1. Once activated, insulin receptor substrate 1 initiates two critical oncogenic signalling pathways: the PI3K/Akt and MAPK/ERK pathways [62,63,64]. The PI3K/Akt pathway enhances cell survival by inhibiting pro-apoptotic proteins such as Bad and Forkhead box O (FoxO), while promoting protein synthesis and cell growth through the activation of mTOR [65,66,67]. The MAPK/ERK pathway directly influences cell cycle progression and stimulates proliferation; sustained and excessive activation of these two pathways collectively disrupts the growth equilibrium of thyroid cells, representing a fundamental mechanism underlying their malignant transformation [68]. Additionally, studies have reported significantly elevated phosphorylation levels of p-Akt and p-

ERK in tumour tissues from thyroid cancer patients with concurrent MASLD compared to those without MASLD. In patients with MASLD, visceral adipose tissue acts as an active endocrine organ, exhibiting a pathologically altered secretory profile. Specifically, the levels of adiponectin, which possesses insulin-sensitising and anti-inflammatory properties, are significantly reduced. Conversely, levels of leptin, which promotes inflammation and cell proliferation, as well as resistin and pro-inflammatory cytokines such as IL-6 and TNF- α , remain persistently elevated. Leptin can activate the Janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3) signalling pathway through its receptor, leading to the upregulation of genes, such as VEGF and Bcl-2, which in turn promotes the proliferation, survival, and angiogenesis of thyroid cancer cells. The diminished levels of adiponectin result in a loss of its antagonistic effect against these pro-carcinogenic signals. Additionally, elevated circulating levels of IL-6 and TNF- α can stimulate thyroid cells directly through paracrine and endocrine mechanisms, while also fostering a local pro-tumour inflammatory microenvironment within the thyroid by activating the STAT3 and NF- κ B pathways, thereby indirectly facilitating tumour initiation and progression [69,70,71].

2.6 MASLD and Breast Cancer

MASLD has been identified as an independent risk factor for breast cancer in postmenopausal women, particularly the oestrogen receptor-positive (ER+) subtype. Comprehensive analyses from systematic reviews and multicentre cohort studies have indicated that women with MASLD have an approximately 1.2 to 1.7 times higher risk of developing breast cancer than those without MASLD; the risk being more pronounced in individuals with MASLD [72,73]. Genetic epidemiological studies employing Mendelian randomisation have established a causal relationship between MASLD and breast cancer risk in women, suggesting that MASLD is not merely a correlative factor but likely plays a direct role in its pathogenic mechanism [74].

In postmenopausal women, a decline in ovarian function results in the adipose tissue becoming the primary source of endogenous oestrogen. In the context of obesity and MASLD, the activity of aromatase (CYP19A1) in visceral adipose tissue markedly increases. This enzyme serves as the rate-limiting factor in the conversion of androgens, such as androstenedione and testosterone, into oestrogens, including oestrone and oestradiol. Consequently, women with MASLD demonstrate abnormally elevated levels of circulating oestrogen. Oestrogen binds to ER in the nuclei of breast cancer cells, activating the classical genomic pathway and initiating the transcription of various cell cycle-related genes, such as Cyclin D1 and c-Myc, which significantly drive the proliferation of ER+ breast cancer cells. Furthermore, oestrogen can rapidly activate non-genomic signalling pathways, in-

cluding MAPK and PI3K, through the membrane-bound G protein-coupled oestrogen receptor, thereby further enhancing pro-proliferative signals. Hyperinsulinaemia may synergise with oestrogen signalling; insulin suppresses the synthesis of sex hormone-binding globulin, increasing the concentration of bioavailable oestrogen in the bloodstream, creating a vicious cycle [75,76,77]. The chronic low-grade inflammatory state induced by MASLD plays a critical role in the initiation and progression of breast cancer. Persistently elevated levels of circulating inflammatory cytokines, such as IL-6 and TNF- α , promote breast cancer cell proliferation, invasion, and metastasis by directly activating the Janus kinase/signal transducer and activator of transcription (JAK/STAT)3 and NF- κ B pathways. More importantly, these cytokines significantly remodel the tumour immune microenvironment. They can induce macrophage polarisation toward the M2 phenotype of TAMs. M2-type TAMs create a potent immunosuppressive environment by secreting inhibitory cytokines, including TGF- β and IL-10, and by expressing programmed death-ligand 1. This process suppresses the activation and function of cytotoxic T cells (CD8⁺ T cells), while promoting the proliferation of regulatory T cells, thereby facilitating tumour immune escape [78,79,80]. Furthermore, free fatty acids derived from adipose tissue can be utilised by breast cancer cells for beta-oxidation, supplying energy for their rapid proliferation, which further enhances the malignant phenotype of the tumour.

2.7 MASLD and Endometrial Cancer

A nationwide cohort study in Korea, which included over 2.3 million young women, demonstrated a significant association between MASLD and an increased risk of early endometrial cancer (EC), revealing a dose-dependent relationship; specifically, greater severity of fatty liver was linked to a higher risk of EC [81]. Additionally, a Chinese cross-sectional study involving 725 patients with EC found that the presence of MASLD was significantly correlated with the risk of cervical stromal invasion, implying that MASLD is involved in cancer initiation and can lead to tumour progression [82]. The relationship between MASLD scores and EC risk varies among different populations. For example, the effects of MASLD are particularly significant in obese women; however, it also elevates cancer risk in non-obese women, suggesting that metabolic dysregulation associated with fatty liver operates independently of obesity [81,83]. Furthermore, MASLD is closely linked to metabolic disorders such as metabolic syndrome and diabetes, which are notable risk factors for EC, complicating efforts to fully delineate its independent impact [84,85]. In summary, as the hepatic manifestation of metabolic syndrome, MASLD plays a crucial role in the pathogenesis of EC, highlighting the clinical importance of its early detection and management as a vital strategy for mitigating EC risk [86,87]. MASLD is closely associated

with IR, a metabolic disorder recognised as a critical mechanism in the development of EC. Fatty liver contributes to IR through various pathways, resulting in disturbances in glucose metabolism and impaired insulin signalling both in the liver and systemically, leading to hyperinsulinaemia. This hyperinsulinaemia exacerbates the pathological progression of MASLD and facilitates the proliferation and malignant transformation of endometrial cells via the IGF-1 signalling pathway. IR prompts compensatory overproduction of insulin by the pancreas, resulting in elevated insulin levels. Increased insulin concentrations can lower sex hormone-binding globulin levels, thereby enhancing the bioavailability of free oestrogen, which further stimulates endometrial cell proliferation. Additionally, elevated levels of insulin and IGF-1 activate signalling pathways, such as phosphoinositide 3-kinase/protein kinase B/mechanistic target of rapamycin (PI3K-AKT-mTOR), which promote cell cycle progression and inhibit apoptosis, thereby driving the initiation and progression of EC [88,89]. Clinically, indices of IR (e.g., TyG index and METS-IR) correlate with the risk of EC, with body mass index serving as a significant mediator in this relationship [90,91]. Furthermore, both IR and metabolic syndrome not only increase the risk of developing EC but are also linked to recurrence risk in patients following conservative treatment. In summary, by inducing IR and hyperinsulinaemia and activating IGF-1 and its downstream signalling pathways, MASLD fosters abnormal proliferation and tumorigenesis of endometrial cells, representing a crucial metabolic pathological mechanism in EC.

Adipocytes and hepatic macrophages within the MASLD microenvironment secrete substantial amounts of pro-inflammatory cytokines, including TNF- α and IL-6, which stimulate hepatic CRP production as an acute-phase protein. These inflammatory mediators can influence distant tissues, such as the endometrium, through endocrine and paracrine mechanisms [92,93]. Research indicates that TNF- α and IL-6 are upregulated in patients with MASLD and are closely linked to clinical stage, tumour grade, and poor prognosis in EC [93,94]. Chronic inflammation associated with fatty liver activates signalling pathways, such as NF- κ B, which promotes tumour cell survival and proliferation while inhibiting apoptosis. Inflammatory mediators, including TNF- α , can stimulate the production of anti-apoptotic proteins in endometrial cancer cells, thereby facilitating immune evasion. Furthermore, chronic inflammation modifies the TME, creating an immunosuppressive state that enhances tumour growth and metastasis [95]. In summary, chronic low-grade inflammation associated with MASLD, through the secretion of pro-inflammatory factors, inhibition of tumour cell apoptosis, and remodelling of the TME, contributes to the initiation and progression of EC. MASLD significantly affects hormone metabolism, resulting in abnormalities in oestrogen metabolism. This disruption leads to elevated systemic oestrogen levels, thereby increasing the risk of EC. Adipose tissue serves as an active

site for oestrogen synthesis and metabolism. Patients with MASLD often present with concurrent obesity and dysfunctional adipose tissue, characterised by increased aromatase activity within adipocytes, which facilitates the conversion of androgens to oestrogens, culminating in abnormally high oestrogen levels [96]. Additionally, liver impairment associated with MASLD adversely affects oestrogen metabolism and clearance, contributing to its accumulation in the body. Oestrogen binds to the ER to mediate endometrial cell proliferation. A prolonged state of oestrogen dominance, particularly when unopposed by progesterone, promotes abnormal endometrial hyperplasia and carcinogenesis [97,98]. Metabolic abnormalities may also influence oestrogen receptor expression; for instance, the expression of ER α in tumour-associated macrophages promotes epithelial-mesenchymal transition and enhances the invasive capacity of tumour cells [95]. Clinical studies have identified abnormally elevated oestrogen levels in patients with MASLD, which positively correlate with the incidence of EC [83]. Furthermore, patients with MASLD frequently exhibit comorbid metabolic syndrome and IR, which further exacerbate hormonal imbalances and create a pro-carcinogenic environment conducive to EC development [98]. Consequently, fatty liver facilitates the initiation and progression of EC by disrupting oestrogen metabolism and receptor expression, resulting in aberrant hormone levels and dysregulation of hormonal signalling pathways.

2.8 MASLD and Renal Cancer

MASLD and metabolic syndrome (MetS) share many metabolic abnormalities. Findings from studies of MetS are therefore useful when considering whether metabolic dysfunction is linked to kidney cancer. In a large prospective cohort, MetS remained associated with a higher risk of kidney cancer after multivariable adjustment (HR = 1.74, 95% CI: 1.28–2.37). Elevated blood pressure, one component of MetS, was also associated with increased risk (HR = 1.74, 95% CI: 1.21–2.51) [99]. That study, however, did not directly assess MASLD in relation to kidney cancer. Among the various RCC subtypes, the relationship between MASLD and ccRCC is the most clearly defined, closely associated with the distinctive metabolic characteristics of ccRCC. A defining metabolic characteristic of ccRCC is the significant accumulation of lipids and glycogen within the cytoplasm. The dyslipidaemic environment associated with MASLD provides abundant “fuel” and “building blocks” for the proliferation of ccRCC cells. Renal cancer cells demonstrate markedly increased fatty acid uptake and depend heavily on fatty acid oxidation (FAO) for ATP production. This metabolic reprogramming is partially driven by the overexpression of peroxisome proliferator-activated receptor gamma (PPAR γ). However, lipotoxicity arises when lipid intake surpasses the cellular capacity for oxidation and storage. Excess lipids, particularly saturated fatty acids, can cause mitochondrial dysfunction, endoplasmic reticu-

lum stress, and significant ROS production. These ROS can inflict damage on both mitochondrial and nuclear DNA, leading to the accumulation of carcinogenic mutations if not adequately repaired. Additionally, lipid metabolic intermediates, such as ceramides, contribute to the induction of resistance to apoptosis and the activation of pro-inflammatory signalling pathways, collectively facilitating the malignant transformation of renal tubular epithelial cells [100,101,102].

Most ccRCC cases are characterised by inactivating mutations or silencing of the von Hippel–Lindau (VHL) tumour suppressor gene [103]. The primary function of the VHL protein is to facilitate the ubiquitin-mediated degradation of HIF- α subunits [104]. When VHL function is lost, HIF- α subunits become constitutively stabilised in renal cancer cells, even under normoxic conditions. This stabilisation activates a range of target genes associated with angiogenesis (e.g., VEGF), glycolysis (e.g., glucose transporter 1 (GLUT1)), and cell proliferation, thereby exemplifying the classic activation of the HIF pathway [105]. Pathological conditions linked to MASLD, particularly insulin resistance and chronic inflammation, can significantly affect the HIF pathway. For example, insulin can stimulate HIF- α synthesis through the PI3K/Akt/mTOR pathway, while inflammatory cytokines such as TNF- α can enhance the transcriptional activity of HIF-1 α . This synergistic interaction further intensifies the pro-oncogenic signalling resulting from VHL loss, particularly in promoting tumour angiogenesis and increasing glycolytic capacity, thereby providing ccRCC with a substantial growth advantage within the metabolic environment of MASLD [106,107].

2.9 MASLD and Prostate Cancer

Retrospective and prospective cohort studies have established a correlation between MASLD and prostate cancer. Research indicates that the incidence of prostate cancer is significantly higher in individuals with MASLD than in those without the condition [15,108]. The relationship between MASLD and prostate cancer varies across populations and ethnicities. Studies have identified an inverse correlation between liver fibrosis scores and prostate cancer incidence in black men, whereas no such association has been found in white men [109]. Additionally, genetic polymorphisms and environmental factors, including dietary habits, may contribute to the varying risks of prostate cancer associated with MASLD across populations [110]. These differences indicate that the epidemiological relationship between MASLD and prostate cancer is complex and requires consideration of multiple factors, including race, genetics, and lifestyle. Aberrations in fatty acid metabolism among patients with MASLD provide both energy support and regulatory signalling for prostate cancer cells. Research indicates that Fatty Acid Binding Protein 5 (FABP5) is upregulated in various cancers, particularly prostate cancer, where

it facilitates fatty acid transport and metabolism, activates transcription factors, and drives tumour growth and metastasis [111,112]. Additionally, Fatty Acid Desaturase 2, located at the major cancer hotspot 11q13 locus, alters fatty acid biosynthesis and influences the development of several cancers, including prostate cancer [113]. Metabolic disturbances associated with fatty liver also involve aberrant expression and activity of key “de novo” lipogenic enzymes in prostate cancer, such as Fatty Acid Synthase, ATP-citrate lyase, and Stearoyl-CoA Desaturase-1. These enzymes facilitate lipid synthesis to meet the energy and membrane component demands of cancer cells [114,115]. Clinical studies have demonstrated an increased risk of prostate cancer in patients with MASLD, with metabolic abnormalities closely linked to biochemical disease [108,109]. In summary, fatty liver promotes metabolic reprogramming in prostate cancer cells by inducing insulin resistance and abnormal fatty acid metabolism, thereby promoting tumour proliferation and progression.

Chronic systemic inflammation induced by MASLD is an important mechanism involved in the development and progression of prostate cancer. Inflammation of adipose and hepatic tissues associated with MASLD results in elevated levels of pro-inflammatory cytokines, such as TNF- α and IL-6, both systemically and within the local microenvironment. These cytokines not only promote inflammatory responses but also activate signalling pathways, including NF- κ B and STAT3, which enhance the proliferation, invasion, and metastatic potential of prostate cancer cells [116,117]. Chronic inflammation contributes to DNA damage and genomic instability in prostate tissues, thereby increasing the risk of tumorigenesis [118]. Furthermore, inflammation-mediated alterations in the immune microenvironment facilitate tumour immune escape by recruiting and polarising macrophages and activating immunosuppressive cells, creating conditions favourable for sustained tumour growth and metastasis [119,120,121]. Research has also demonstrated that the pro-inflammatory state associated with MASLD induces a local blood coagulation cascade within the prostate tissue, establishing a thrombo-inflammatory state that promotes abnormal proliferation and early neoplastic transformation of prostate epithelial cells [117,121]. Concurrently, immune dysregulation driven by chronic inflammation results in dysfunctional immune cells within the tumour microenvironment, suppressing antitumour immune responses and accelerating the malignant progression of prostate cancer [122,123]. Thus, chronic inflammation initiated by MASLD and the subsequent alterations in the immune microenvironment are central mechanisms in the initiation and development of prostate cancer. The influence of MASLD on androgen metabolism and the associated endocrine environment is crucial in prostate carcinogenesis. MASLD can alter hepatic metabolism and clearance of androgens, thereby modulating the circulating levels of free androgens, which in turn affect the growth and differentiation of prostate cancer cells [124,125]. In the

context of fatty liver and obesity, the levels of metabolic hormones such as adiponectin and leptin are typically altered, with adiponectin decreasing and leptin increasing. These hormones affect the development and progression of prostate cancer by modulating inflammatory responses, cell proliferation, and apoptosis [126]. Research suggests that adiponectin possesses anti-inflammatory and anti-tumour properties, and its reduction correlates with an increased risk of prostate cancer, whereas leptin facilitates tumour cell proliferation and angiogenesis. Moreover, the androgen receptor (AR) signalling pathway may be dysregulated in patients with MASLD, characterised by an increased expression of AR variants that promote the development of castration-resistant prostate cancer [127,128]. Androgen receptor inhibitors such as EPI-001, which are used in prostate cancer treatment, have also demonstrated potential therapeutic effects against MASLD, indicating that hormone levels and AR signalling are critical components in the interplay between MASLD and prostate cancer [128]. In summary, fatty liver affects the endocrine environment in prostate cancer by influencing androgen metabolism and metabolic hormone levels, thereby facilitating tumour initiation and progression.

2.10 Impact of MASLD Treatment on Extrahepatic Cancer Risk

Emerging evidence suggests that treatment of MASLD may have implications beyond liver-specific outcomes and could potentially modify the risk of extrahepatic cancer. Lifestyle interventions remain the cornerstone of MASLD management because dietary modifications, increased physical activity, and sustained weight loss can improve hepatic steatosis, insulin resistance, and systemic inflammation. Although direct evidence in MASLD populations with cancer incidence as the primary endpoint remains limited, studies in the broader field of obesity indicate that intentional weight loss, particularly when substantial and durable, may reduce the incidence of several obesity-related malignancies. Bariatric metabolic surgery has been associated with reduced cancer incidence and mortality in observational studies [129]. Among the available pharmacotherapies, GLP-1 receptor agonists (GLP-1RAs) have emerged as promising therapeutic agents for MASLD because of their well-established effects on weight reduction, glycaemic control, and hepatic steatosis, as well as their pleiotropic anti-inflammatory, immunomodulatory, and hepatoprotective properties [130]. Mechanistic studies suggest that GLP-1RAs modulate cytokine profiles, regulate macrophage polarisation, attenuate hepatic stellate cell activation, and improve lipid metabolism and mitochondrial function through the gut-liver axis [131]. Clinically, GLP-1RAs provide cardiovascular and renal benefits, and observational data further suggest that their use may be associated with lower risks of cirrhosis, hepatic decompensation, and certain obesity-related cancers, although these observations are

hypothesis generating and non-specific to MASLD [132]. Overall, GLP-1RAs may act as multi-system modulators that influence MASLD pathophysiology and related comorbidities beyond their metabolic effects, underscoring the need for prospective liver-focused trials to define their broader therapeutic value [133]. In contrast, the current evidence for sodium-glucose cotransporter 2 inhibitors remains inconclusive with respect to cancer prevention, and no definitive chemopreventive effect has yet been established. Similarly, although liver-directed therapies, such as resmetirome, improve the important metabolic and histological features of MASLD/MASH, their long-term effects on extrahepatic cancer risk remain unknown. Therefore, the concept of “treatment as prevention” in MASLD is biologically plausible and clinically attractive; however, it still requires validation in prospective studies and randomised trials with cancer-related endpoints [134,135,136,137,138].

2.11 Potential Associations With Other Extrahepatic Malignancies

In addition to gastrointestinal and hormone-related cancers, MASLD may be linked to other malignancies, including lung, bladder, and other genitourinary cancers, and possibly to haematological malignancies. However, compared with colorectal, pancreatic, breast, and endometrial cancers, evidence for these tumour types is less consistent and remains largely observational. Mechanistically, systemic insulin resistance, chronic inflammation, adipokine imbalance, immune dysregulation, and altered lipid metabolism may explain these associations. However, these links should be considered exploratory rather than conclusive, and further prospective studies are required to determine their strengths, clarify causality, and identify organ-specific mechanisms.

3. Summary and Outlook: Role of MASLD as a Driver of Extrahepatic Cancers and Future Directions

The association between MASLD and extrahepatic cancers highlights the close connection between metabolic diseases and oncogenesis. The evidence reviewed in this article suggests that MASLD should not be regarded merely as an isolated liver disorder, but rather as a systemic metabolic condition that may contribute to tumour development in extrahepatic organs. This effect is likely mediated by multiple interacting mechanisms, including insulin resistance/hyperinsulinemia, chronic low-grade inflammation and immune dysregulation, altered lipid metabolism and metabolic reprogramming, sex hormone imbalance, and disruption of the gut microbiota-liver axis (Figs. 2,3). Together, these mechanisms may create a biological milieu that supports the initiation and progression of extrahepatic tumours. Therefore, future research and clinical efforts should focus on translating these mechanistic insights into

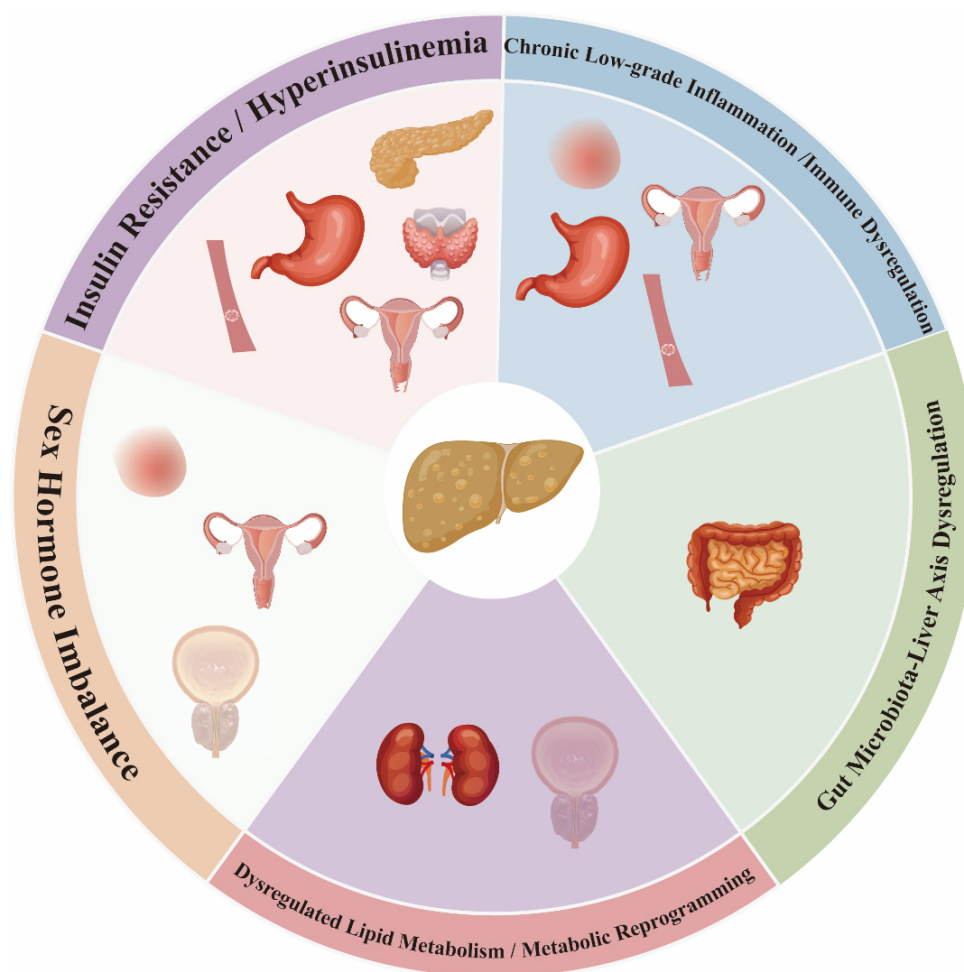


Fig. 2. Pathogenic mechanisms of MASLD: an intertwined network promoting extrahepatic cancer. The figure was prepared using Adobe Illustrator 2025 (Adobe Inc., San Jose, CA, USA).

practical risk assessments, prevention, and treatment strategies.

3.1 Deepening and Integrating Mechanistic Research: From Association to Causality

Current evidence has revealed strong epidemiological links and several plausible molecular pathways; however, many of the underlying causal mechanisms and intercellular signalling processes remain unclear. Future studies should take advantage of modalities such as single-cell sequencing, spatial transcriptomics, and metabolomics to define molecular interactions between MASLD-affected liver and specific tumour microenvironments at single-cell resolution. One important question is how liver-derived pathogenic hepatokines in MASLD, such as fetuin-A and selenoprotein P, influence the behaviour of cell populations in distant organs, including cancer stem cells and immunosuppressive cells, through circulation. The integration of multi-omics data may also help identify key molecular links between metabolism and cancer, and support the discovery of promising therapeutic targets.

3.2 Development and Validation of Biomarkers: Enabling Early Warning and Risk Stratification

Because patients with MASLD may be at increased risk of cancer, non-invasive and accurate tools for risk prediction are needed. Future studies should focus on identifying and validating biomarkers that can help predict the risk of extrahepatic cancers in this population. Potential approaches include blood-based biomarkers, such as circulating non-coding RNAs (e.g., lncRNAs and circRNAs), proteomic signatures, and small metabolic molecules (e.g., specific bile acids and sphingolipids), as well as imaging biomarkers. In particular, artificial intelligence (AI) may be used to analyse routine imaging data, including abdominal ultrasound and CT, to assess liver fat content, fibrosis stage, and visceral fat distribution and to support the development of tumour risk prediction models. The goal is to integrate these multimodal data into a practical risk stratification system that can facilitate early identification and more targeted management of high-risk patients with MASLD.

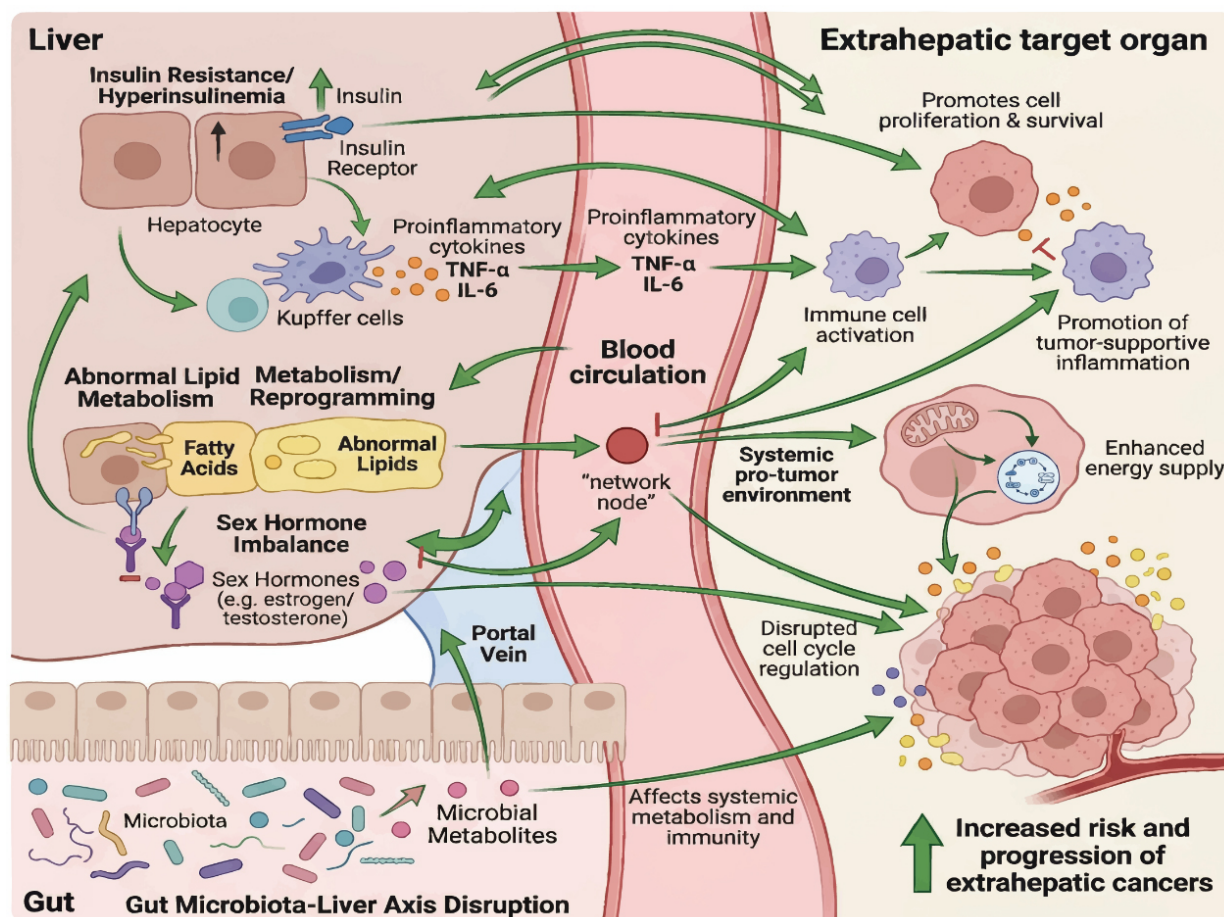


Fig. 3. Multidimensional metabolic, inflammatory, hormonal, and microbial crosstalk. MASLD may promote extrahepatic carcinogenesis through interconnected systemic and organ-specific pathways. As shown, insulin resistance/hyperinsulinemia, dysregulated lipid metabolism, proinflammatory cytokine signaling, sex hormone imbalance, and gut-liver axis dysfunction together contribute to a systemic pro-tumorigenic milieu. These alterations may influence immune activation, tumor-promoting inflammation, energy metabolism, and cell-cycle regulation in extrahepatic organs, thereby facilitating extrahepatic carcinogenesis and tumor progression. Arrows indicate hypothesized mechanistic links. Abbreviations: MASLD, metabolic dysfunction-associated steatotic liver disease; TNF- α , tumor necrosis factor- α ; IL-6, interleukin-6. The figure was prepared using Adobe Illustrator 2025 (Adobe Inc., San Jose, CA, USA).

3.3 Intervention Strategies Targeting Metabolic Pathways: From Controlling Metabolism to Preventing Cancer

An important next step in clinical translation is to determine whether existing metabolic drugs can lower the risk of extrahepatic cancers. Retrospective studies suggest that agents such as sodium-glucose cotransporter 2 inhibitors, GLP-1 receptor agonists and PPAR γ agonists may offer benefits beyond improving liver fat and inflammation, including a possible reduction in cancer risk. To clarify this, large-scale prospective randomised controlled trials are needed, with cancer incidence in patients with MASLD included as a major clinical outcome. In addition, gut microbiota-targeted approaches, such as prebiotics, probiotics, and faecal microbiota transplantation, together with emerging anti-fibrotic therapies, deserve further evaluation as potential modulators of the “gut-liver-tumour axis”.

3.4 Establishing Multidisciplinary Team Management Models: Revolutionising Clinical Practice

From a clinical management perspective, a broader and more integrated strategy is needed for MASLD. We propose stronger collaboration among hepatology, endocrinology, oncology, nutrition, and gastroenterology to support the multidisciplinary management of MASLD. Clinicians should consider the potential elevation in cancer risk among patients with MASLD and incorporate this into long-term management plans. Such plans should extend beyond liver-focused care to include individualised metabolic interventions, such as diet, exercise, and pharmacotherapy, along with risk-based cancer screening. The frequency and type of screening procedures, including colonoscopy, thyroid ultrasonography, and mammography, should be determined according to each patient’s risk profile. This integrated “metabolism-oncology” approach may offer a useful framework for improving clinical outcomes.

4. Discussion

MASLD is now widely recognised as a multi-system metabolic disorder rather than a disease confined to the liver, and accumulating evidence links it to an increased risk of several extrahepatic cancers. However, these associations vary in strength and consistency across tumour types. The evidence is relatively stronger for several gastrointestinal malignancies, particularly colorectal and pancreatic cancer, whereas findings for thyroid, breast, endometrial, renal, and prostate cancers remain more heterogeneous. Therefore, the relationship between MASLD and extrahepatic cancers should be evaluated according to cancer type and the quality of the available evidence.

MASLD should not be regarded as a common liver disease but as a heterogeneous metabolic-inflammatory disorder with multiple underlying mechanisms that influence both disease progression and treatment response. Recent reviews suggest that insulin resistance, adipose tissue dysfunction, subclinical inflammation, altered hepatokine signalling, mitochondrial dysfunction, disturbances in the gut-liver axis, and genetic susceptibility all contribute to hepatic steatosis, necroinflammation, fibrosis, and extrahepatic complications. This heterogeneity has important clinical implications, as it may help explain why patients respond differently to treatment and why improvements in liver outcomes do not always coincide with changes in body weight or cardiometabolic risk factors. Accordingly, therapeutic strategies should move beyond describing MASLD primarily in terms of prevalence and instead focus on mechanism-based approaches, including sustained weight loss, incretin-based therapies, and other emerging agents, while considering the different hepatic and systemic effects of treatment.

The link between MASLD and extrahepatic carcinogenesis is likely driven by a combination of systemic and organ-specific mechanisms. IR, chronic low-grade inflammation, dysregulated lipid metabolism, hormonal imbalance, and gut-liver axis dysfunction may together create a pro-tumorigenic environment. However, epidemiological associations do not necessarily imply causality, as most available studies are observational, and the effects of shared risk factors, including obesity, type 2 diabetes, metabolic syndrome, ageing, and lifestyle, cannot be fully ruled out. Therefore, MASLD may reflect underlying systemic metabolic dysfunction while also contributing to tumour development, although mechanistic evidence is still insufficient to establish a clear causal role in many cancer types.

From a clinical standpoint, these findings underscore the need for comprehensive metabolic assessment and multidisciplinary care in patients with MASLD. Lifestyle intervention and reduction of metabolic risk may improve not only liver-related outcomes but also cancer prevention, although direct evidence that treating MASLD lowers the risk of extrahepatic cancers is still limited. Current studies are also limited by heterogeneity in diagnostic criteria, study

design, and the extent of mechanistic research across different tumour types. Future research should clarify causal relationships, identify organ-specific pathways and biomarkers, and determine whether effective treatment of MASLD can reduce the incidence of extrahepatic cancers.

5. Conclusion

In summary, recognising the systemic effects of MASLD, particularly its role in increasing cancer risk, is important for advancing integrated prevention and management at the interface of metabolism and oncology. MASLD represents an important link between metabolic disorders, such as obesity and diabetes, and the growing burden of cancer. A better understanding of its biological mechanisms, together with the development of practical clinical strategies, such as early risk identification, pharmacological treatment, and multidisciplinary care, may help reduce the cancer burden associated with metabolic diseases.

Key Points

- MASLD is increasingly recognized as a systemic metabolic disorder rather than a liver-limited disease, and growing evidence suggests that it is associated with an increased risk of multiple extrahepatic cancers.
- The relationship between MASLD and extrahepatic carcinogenesis is likely mediated by multiple interconnected mechanisms, including insulin resistance, chronic inflammation, lipid metabolic dysregulation, hormonal imbalance, and gut-liver axis disturbance, together with organ-specific susceptibility.
- The epidemiological evidence appears relatively stronger for gastrointestinal cancers, particularly colorectal and pancreatic cancer, whereas the associations with thyroid, breast, endometrial, renal, and prostate cancers remain less consistent and require further validation.
- MASLD may act both as a marker of systemic metabolic dysfunction and as a potential promoter of tumor development; however, most available studies remain observational, and direct causal inference should therefore be made with caution.
- A better understanding of the links between MASLD and extrahepatic cancers may improve risk stratification and multidisciplinary management, while future studies should focus on clarifying causal relationships, identifying reliable biomarkers, and determining whether effective MASLD treatment can reduce cancer risk.

Availability of Data and Materials

Not applicable.

Author Contributions

SP, JQ and QZ conceived the idea and drafted the manuscript. Manuscript important revisions, figures preparation, and content adjustments were completed by ZK, HD, XW, HC, YS, YN, and YZ. All authors gave final approval

of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

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