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Review

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High-Fructose Corn Syrup on Inflammation and Cancer

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Abstract

High-fructose corn syrup (HFCS), a widely used sweetener in processed foods and beverages since the 1970s, has garnered significant attention for its potential role in promoting metabolic disorders and cancer. Unlike glucose, fructose is primarily metabolized in the gut, where it stimulates *de novo* lipogenesis, promotes insulin resistance, and contributes to hepatic steatosis. These metabolic disturbances are strongly associated with chronic low-grade inflammation, a well-established risk factor for tumor development and progression. Emerging evidence suggests that HFCS contributes to a pro-inflammatory environment through upregulation of macrophage activation, increased cytokine production, and disruption of gut microbiota homeostasis, thereby impairing intestinal barrier integrity and promoting systemic inflammation. Animal studies have shown that HFCS consumption induces greater insulin resistance and adipose tissue inflammation compared to high-fat diets. Recent research highlights the direct influence of HFCS on cancer biology, beyond its indirect effects through obesity and metabolic disorders. Preclinical models demonstrate that HFCS intake accelerates tumor growth in colorectal, breast, and melanoma tumor models, independent of obesity. Mechanistically, fructose metabolism supports cancer cell proliferation via enhanced glycolysis, lipogenesis, and nucleotide synthesis through the pentose phosphate pathway. Fructose also suppresses necroptosis in hypoxic conditions and may promote metastasis via the generation of lipid mediators like lysophosphatidylcholine (LPC) and the upregulation of fructose transporters such as glucose transporter 5 (GLUT5). Diets rich in HFCS have been shown to activate the insulin/insulin-like growth factor 1 (IGF-1) signaling pathway, leading to enhanced tumor growth and reduced apoptosis. Epidemiological data link high fructose consumption with increased risk for in colorectal, pancreatic, and breast cancers in addition to poorer prognosis in these patients. However, findings remain heterogeneous, likely due to variability in fructose sources, dietary patterns, and host factors. Given the widespread dietary exposure to HFCS, understanding its metabolic, inflammatory, and oncogenic effects is critical. This review synthesizes current evidence linking HFCS to cancer pathogenesis and underscores the urgent need for further research into fructose-specific mechanisms and their relevance to cancer prevention and therapeutic strategies.

Keywords: High-Fructose Corn Syrup; HFCS; Inflammation; Cancer

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Introduction

High-fructose corn syrup (HFCS) has been extensively utilized as a sweetener in processed foods and beverages since the 1970s, primarily due to its cost-effectiveness and sweetness comparable to sucrose [1]. Its widespread adoption coincided with a notable increase in obesity rates in the United States, suggesting a potential link between HFCS consumption and the obesity epidemic.

HFCS is composed of varying ratios of fructose and glucose, with common formulations including HFCS-42 and HFCS-55, containing approximately 42% and 55% fructose, respectively [2]. Although HFCS is generally described as containing 42% or 55% fructose, independent laboratory analyses have demonstrated that some commercially available sweetened beverages actually contain higher fructose-to-glucose ratios, ranging from 60% to 65%. Importantly, food labels do not disclose the exact fructose content, and the actual composition may differ from what is generally recognized as safe [3, 4]. Unlike glucose, fructose is predominantly metabolized in the gut, where it can promote *de novo* lipogenesis (DNL), leading to increased triglyceride synthesis, insulin resistance, and hepatic steatosis. Recent evidence indicates that the small intestine, rather than the liver, is the primary site of initial fructose metabolism. Most absorbed fructose is converted to glucose and organic acids by enterocytes before reaching the portal circulation. Fructose that exceeds an individual's intestinal absorptive and metabolic capacity "spills over" first into the gut lumen, altering the intestinal environment and microbiota, and, when further exceeded, into the liver where it is metabolized [4-9]. These metabolic disturbances are associated with chronic low-grade inflammation, a recognized contributor to the development and progression of various type of cancers [5].

Recent studies have elucidated mechanisms by which excessive fructose intake may facilitate tumorigenesis. For instance, fructose has been shown to induce inflammatory activation in macrophages, enhancing the pro-inflammatory state of the tumor microenvironment. In addition to its metabolic effects, unabsorbed fructose in the gut has been shown to undergo non-enzymatic fructosylation of peptides, including incretins, leading to the *in situ* formation of fructose-derived advanced glycation end-products (FruAGEs). These FruAGEs exhibit high affinity for receptors of advanced glycation end-products (RAGEs), thereby promoting pro-inflammatory signaling. This mechanism, known as the "Fructositis hypothesis," has been supported by a series of studies, with Yuan et al providing the most recent evidence that FruAGEs are generated during simulated gastrointestinal digestion [10]. Furthermore, epidemiologic evidence links HFCS intake with disproportionately higher asthma risk among young Black adults, further supporting a role of FruAGEs in immune and inflammatory responses [11]. Additionally, fructose can contribute to the metabolic reprogramming of cancer cells, supporting their proliferation and survival. Animal models have demonstrated that high-fructose diets can exacerbate tumor growth in colorectal cancer, independent of obesity [5, 12, 13].

Furthermore, epidemiological data suggest a correlation between high intake of sugar-sweetened beverages, often containing HFCS, and increased cancer risk [14, 15]. These findings underscore the importance of understanding the role of dietary sugars in cancer development.

Given the pervasive presence of HFCS in the modern diet and its potential implications in cancer biology, this article aims to comprehensively review the current evidence linking HFCS consumption to inflammation and cancer. We will explore the metabolic pathways influenced by fructose, its impact on inflammatory processes, and the resultant effects on carcinogenesis.

Metabolism and Absorption of HFCS

HFCS, a mixture of free fructose and glucose, exhibits unique metabolic characteristics distinct from those of glucose. Fructose is primarily absorbed via the GLUT5 transporter in the small intestine, where it is largely converted to glucose and organic acids by enterocytes. When the absorptive and metabolic capacity of the intestine is exceeded, the remaining fructose "spills over" into the liver for further metabolism [6]. Unlike glucose, fructose does not directly stimulate insulin secretion and bypasses the rate-limiting steps of glycolysis, thereby entering metabolic pathways that promote DNL. In addition, unabsorbed fructose in the gut can interfere with incretin signaling by fructosylating and deactivating glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP), which may further contribute to insulin insufficiency [16, 17].

Recent studies have highlighted that excessive intake of HFCS is associated with hepatic fat accumulation, insulin resistance, dyslipidemia, and elevated serum uric acid levels [17]. Recent studies have also provided new insights into the hepatic effects of excessive fructose consumption. Unlike sucrose, HFCS represents a relatively recent introduction into the food supply, with widespread adoption occurring in the United States during the early 1980s. Moreover, independent laboratory analyses indicate that some commercially available sweetened beverages may contain fructose-to-glucose ratios exceeding the commonly cited 55%, thereby increasing excess-free-fructose exposure beyond levels generally recognized as safe. Such formulations can promote fructose malabsorption and altered gut health, mechanisms increasingly implicated across chronic diseases [18]. Ecologically, HFCS production and use rose steeply from 1980 through the late 1990s in the USA, overlapping with rising incidence patterns observed for several cancers, including liver and pancreatic cancer, and with increasing colorectal cancer incidence among younger adults; these site-specific trends warrant further investigation into potential links with excess-free-fructose exposure [19, 20]. One such study made healthy male participants consume beverages sweetened with either fructose or sucrose for 8 weeks and demonstrated a significant increase in hepatic DNL [21]. Moreover, multiple ^{1}H-magnetic resonance spectroscopy (MRS)-based studies have shown that fructose-containing beverages contribute to an increased risk of nonalcoholic fatty liver disease (NAFLD), even over short durations of intake [22-24].

Fructose metabolism rapidly depletes intracellular ATP, leading to increased uric acid production, which has been implicated in hypertension and renal dysfunction. Adolescents with high consumption of HFCS-sweetened beverages were found to have significantly elevated serum uric acid and triglyceride concentrations [25]. However, meta-analyses of isocaloric substitution trials have suggested that fructose may not exert adverse effects on low-density lipoprotein (LDL) cholesterol or glycemic indices under conditions of energy balance [26]. It is important to note, however, that many of these studies were conducted by industry-sponsored groups with potential conflicts of interest. A more recent systematic review and meta-analysis from the same research group, focusing on fructose-containing foods and inflammatory biomarkers, found that eight out of 10 trials including fructose or HFCS showed significant adverse effects, whereas the two that did not excluded individuals with fructose malabsorption either directly or indirectly [27]. No significant effects were observed in studies of fruit or most fruit juices, except apple juice, which is particularly high in unpaired fructose. Collectively, these findings suggest that the distinguishing factor may be excess unpaired fructose rather than energy balance *per se*.

Recent research also suggested that variability in intestinal fructose absorption, potentially influenced by GLUT5 expression, can result in malabsorption and subsequent delivery of fructose to the colon *in vitro* [28]. This can lead to gut microbiota dysbiosis, contributing to impaired intestinal barrier function and systemic low-grade inflammation - factors increasingly recognized in the pathogenesis of metabolic disorders and potentially cancer. In addition, gut-resident advanced glycation end-products (AGEs) themselves have been associated with gut dysbiosis, further supporting a link between dietary fructose, FruAGE formation, and altered intestinal microbial ecology [29-32].

In animal models, HFCS consumption has been shown to induce greater insulin resistance and adipose tissue inflammation than high-fat diets [33]. Short-term consumption of HFCS-sweetened beverages has been shown to increase hepatic fat accumulation and reduce insulin sensitivity, indicating a potential risk for the development of metabolic disorders [34]. Moreover, fructose intake has been associated with increased visceral adiposity, adverse alterations in circulating lipid profiles, and further reductions in insulin sensitivity, all of which may contribute to the pathogenesis of metabolic syndrome [35]. Furthermore, the lack of stimulation of satiety hormones such as insulin and leptin by fructose may facilitate excess caloric intake and weight gain, reinforcing its obesogenic potential. Beyond overconsumption, however, recent evidence emphasizes that the unique presence of unpaired fructose in HFCS can exceed intestinal absorptive capacity, leading to malabsorption, altered gut microbial composition, and inflammatory responses. In animal models, dietary fructose has been shown to worsen colitis through gut microbiota-dependent mechanisms [36]. Clinically, fructose malabsorption is prevalent among patients with irritable bowel syndrome even after excluding small intestinal bacterial overgrowth, supporting the pathophysiological relevance of excess unabsorbed fructose [37].

Despite its metabolic drawbacks, fructose possesses a low glycemic index. In controlled settings, moderate fructose intake (< 60 g/day) has been shown to reduce HbA1c levels in patients with type 2 diabetes without adversely affecting fasting glucose or insulin [26]. However, it should be noted that these trials did not systematically assess fructose malabsorption status among participants, which may represent an important limitation given that malabsorption can significantly modify metabolic and inflammatory outcomes. Mechanistically, fructose may exert glucose-sparing effects by enhancing glucokinase activity, promoting glycogen synthesis, and suppressing hepatic glucose output.

HFCS and Inflammation

Emerging evidence highlights a mechanistic link between HFCS consumption and chronic low-grade inflammation: a key component of the pathophysiology of metabolic syndrome and type 2 diabetes [1, 38, 39]. Several studies have reported that excessive fructose intake elevates biomarkers of inflammation and oxidative stress, including reactive oxygen species and proinflammatory cytokines such as Toll-like receptor 4 (TLR-4), C-reactive protein (CRP), interleukin (IL)-6, E-selectin, and plasminogen activator inhibitor 1 (PAI-1) [39-44]. In rodent models, HFCS has been shown to induce more pronounced adipose tissue inflammation than high-fat diets, in part by enhancing proinflammatory macrophage infiltration and promoting insulin resistance via ghrelin receptor-mediated pathways [33]. Furthermore, deficiency of the ghrelin receptor (GHS-R) has been shown to attenuate HFCS-induced adipose tissue inflammation and insulin resistance [33]. Activation of peroxisome proliferator-activated receptor-delta (PPAR-δ) has also been shown to mitigate HFCS-induced renal and systemic inflammation [45, 46].

Fructose also appears to modulate immune signaling through the upregulation of multiple cytokines, including interferon (IFN)-γ, IL-1β, IL-6, tumor necrosis factor (TNF)-α, and IL-2, in both adipose and skeletal muscle tissues [47, 48].

In addition to these systemic effects, chronic fructose exposure has been implicated in gut microbiota dysbiosis. Studies have demonstrated that excessive intake of fructose and artificial sweeteners reduces microbial diversity and shifts microbial composition toward proinflammatory compositions, potentially compromising intestinal barrier integrity and contributing to systemic endotoxemia [49-51].

These microbiota-mediated changes may link HFCS intake to inflammation-associated carcinogenesis. Inflammatory transcription factors such as signal transducer and activator of transcription 3 (STAT3) and nuclear factor-κB (NF-κB), which are activated downstream of microbial and metabolic signals, play central roles in promoting tumorigenesis under chronic inflammatory conditions [52-54]. Collectively, these findings underscore the proinflammatory and immunomodulatory potential of HFCS in the development of metabolic and neoplastic diseases.

HFCS and Cancer

Recent research suggests that HFCS may directly contribute to cancer development and progression beyond its indirect effects through obesity and metabolic disorders. Epidemiologically, conditions strongly linked to excessive fructose intake - such as obesity and type 2 diabetes - are well-established risk factors for multiple cancers, including colorectal, pancreatic, breast, liver, and endometrial cancers [5, 55].

One of the key mechanisms by which HFCS promotes cancer is the creation of a metabolic environment favorable to tumorigenesis. HFCS-rich diets increase blood glucose and insulin levels, activating the insulin/IGF-1 signaling pathway that enhances tumor growth and inhibits apoptosis [56-59]. This pathway, through phosphatidylinositol-3-kinase-Akt-mammalian target of rapamycin (PI3K-Akt-mTOR) activation, supports cancer cell proliferation and metabolic reprogramming.

Preclinical studies have demonstrated that HFCS can directly promote tumor growth. Oral administration of HFCS (45% glucose, 55% fructose) in adenomatous polyposis coli (APC) mutant mice has been shown to significantly increase tumor size and grade, independent of obesity or presence of metabolic syndrome. Within cancer cells, rapid fructose metabolism enhances glycolysis and fatty acid synthesis, thereby fueling cell proliferation [55].

Furthermore, a study found that HFCS consumption promoted tumor growth in animal models of melanoma, breast, and cervical cancer [13]. Interestingly, this effect did not stem from fructose utilization by the tumor cells themselves, but rather from liver metabolism of fructose into lipid mediators such as LPC, which supported tumor cell growth.

Additionally, in human colorectal cancer cell lines (Caco-2 and HT29), fructose was shown to inhibit receptor-interacting protein (RIP)-dependent necroptosis under hypoxic conditions, thereby promoting tumor cell survival [60]. This effect was linked to enhanced glycolytic activity, suggesting that fructose may aid metabolic adaptation in the tumor microenvironment.

Enzymes involved in fructose metabolism, such as ketohexokinase (KHK), and the fructose transporter GLUT5, have been implicated in cancer cell growth and chemoresistance [61, 62]. Inhibiting their expression has been proposed as a strategy to suppress tumor progression.

In pancreatic cancer cells, fructose has been shown to promote nucleotide synthesis via the non-oxidative branch of the pentose phosphate pathway (PPP), particularly through upregulation of transketolase (TKT) [63]. This enables tumor cell proliferation even under glucose-limited conditions. Targeting fructolytic enzymes such as KHK-C has been proposed as a therapeutic target to suppress tumor growth in colorectal and liver cancers [57].

Overexpression of fructose transporters such as GLUT5 (SLC2A5) has been observed in breast, colorectal, lung, and pancreatic cancers [64, 65], suggesting a role for fructose metabolism in enhancing tumor invasion and metastatic potential.

Additionally, an autopsy study of lung cancers revealed that expression of GLUT3 and GLUT5 was elevated in liver metastases compared to primary tumors, suggesting that fructose metabolism may support survival and proliferation in metastatic sites [66].

Epidemiological studies have yielded mixed findings on the association between fructose intake and cancer risk. Positive associations have been reported for colorectal [67, 68], pancreatic [69], and breast cancers [70], while studies on prostate and lung cancer have shown negative or null associations [59, 71]. These discrepancies may stem from differences in fructose sources (e.g., natural vs. synthetic), dietary backgrounds, and individual microbiome profiles. Another potential limitation of epidemiological studies is time-varying confounding, as older participants typically consume fewer HFCS-sweetened beverages than younger individuals. Consequently, studies restricted to older cohorts may underestimate the true long-term cancer risk associated with HFCS intake. Longitudinal studies that begin in younger populations and follow participants over time are therefore likely to provide more accurate assessments. Consistent with this, US CDC data demonstrate that sugar-sweetened beverage intake decreases with age.

Interestingly, patients with pancreatic cancer have been found to have fasting serum fructose levels three times higher than healthy individuals [72]. Furthermore, in stage III colorectal cancer patients, higher total fructose intake has been associated with worse recurrence-free survival [73].

Taken together, these findings support that HFCS and fructose may influence multiple aspects of cancer biology - including tumor metabolism, proliferation signaling, invasion, and metastasis. Future research should aim to distinguish the effects of fructose metabolism itself from those of excess caloric intake and identify subgroups of patients who may be particularly sensitive to fructose-driven tumor progression.

Conclusion

HFCS is a widely used sweetener in modern diets, and exerts profound effects on metabolic health and carcinogenesis through a complex network of pathways. Beyond its well-established association with obesity and insulin resistance, emerging evidence highlights a direct role for HFCS and fructose in promoting chronic inflammation, modulating immune responses, and facilitating cancer cell proliferation, survival, and metastasis.

Fructose metabolism supports tumor growth through enhanced glycolysis, lipogenesis, and nucleotide synthesis, particularly under nutrient-deprived or hypoxic conditions. Inflammatory and microbiota-mediated pathways further exacerbate the tumor-promoting environment, linking dietary sugar intake to oncogenic signaling cascades. Although epidemiological findings remain mixed, studies have consistently implicated high fructose intake in the increased risk and poor prognosis of several cancer types, including colorectal and pancreatic cancer.

Given the pervasive consumption of HFCS in processed foods and beverages, these findings underscore the urgent need for public health interventions, nutritional education, and further mechanistic studies. Future research should focus on identifying vulnerable populations, characterizing fructose-specific metabolic reprogramming in tumors, and exploring dietary modification as an adjunct to cancer prevention and therapy.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Author Contributions

TA: conceptualization and writing - original draft; GO, KH, and OM: writing - review and editing; KT: supervision and writing - review and editing.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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