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Sex differences in hepatocellular carcinoma

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Abstract

Disparities in the prevalence, progression and prognosis of hepatocellular carcinoma between males and females are well documented, which stem from a complex interplay of various factors. Sex-specific lifestyle, behavioral and psycho-socioeconomic influences, combined with intrinsic hormonal and genetic differences, significantly impact the process of hepatocarcinogenesis. These factors are further augmented by epigenetic mechanisms and co-factors such as hepatitis B and C infections, and metabolic dysfunction-associated steatotic liver disease. Further research is required to elucidate the mechanisms driving these clear sex differences, in order to optimize future prevention and treatment strategies.

Keywords: Hepatocellular carcinoma, sex, metabolic dysfunction-associated steatotic liver disease

INTRODUCTION

Hepatocellular carcinoma (HCC) represents an estimated 85% of all liver malignancies of primary origin, and is a leading contributor to cancer mortality and morbidity worldwide. Globally, it is the third major cause of cancer death and ranks sixth in frequency of diagnosis[1]. HCC often develops in the context of underlying liver cirrhosis and has been well-documented to disproportionately affect men. In men, the HCC incidence and mortality rates are 2 to 4 times higher than those in women[2], making it the second leading cause of cancer-related deaths among men[1].

Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV), heavy alcohol consumption, and metabolic dysfunction-associated steatotic liver disease (MASLD) are well-established risk factors for HCC development. Worldwide, HBV remains the predominant cause of HCC in men and HCV in women[3]. However, the implementation of vaccinations and effective and readily available antiviral treatment has reduced the proportion of HCCs resulting from chronic HBV and HCV. Antivirals have also enhanced long-term survival outcomes in patients with HBV- or HCV-associated HCC who receive curative surgical intervention[4].

On the other hand, MASLD has become the fastest-growing contributor to HCC for both men and women worldwide[5,6]. The incidence and mortality of metabolic-associated steatohepatitis (MASH) HCC in females approaches those of males, in contrast to all other etiologies of liver disease where mortality in males far exceeds females[5]. This trend is also seen in the non-cirrhotic HCC cohort, which encompasses 20% of all HCCs, where cryptogenic/MASLD non-cirrhotic HCC patients have a more balanced sex ratio compared to other etiologies[7]. The superimposed socioeconomic and cultural factors further influence risk factor exposure, accessibility to healthcare, and treatment options, creating a complex interplay of inherent and external variables and thus making it difficult to pinpoint the specific impact of a person's sex on HCC.

Sex disparities in the incidence, progression, response to treatment, and prognosis of HCC are well documented but remain poorly understood, and may only be partially explained by the epidemiological distribution of HCC risk factors. These differences are likely multifactorial [Figure 1] and involve sex-specific lifestyle and socio-behavioral influences, metabolic, hormonal, and genetic factors that are further augmented by co-factors such as HBV/HCV and MASLD.

SCREENING AND SURVEILLANCE

Behavioral differences between the sexes regarding compliance with HCC surveillance are modifiable factors that impact the early detection of HCCs and subsequent chances of cure. In a large retrospective analysis of Asian patients, it was found that compared to males, females with HCC were significantly more compliant to undergoing HCC surveillance and, therefore, tended to be diagnosed with earlier-stage HCC, corresponding to increased overall survival compared to males[8]. This is in keeping with a population-based cohort study in the United States, which showed that young females are more likely to undertake and adhere to frequent HCC surveillance[9]. This may be related to the differing attitudes toward health awareness, risk perception, and health seeking behavior. The reluctance to seek healthcare in men, especially younger men, may be attributed to conformity to masculinity[10]. On the other hand, healthcare exposure and resultant utilization are arguably greater in women, who inherently have more frequent contact with health services in general[11]. This is primarily due to encounters regarding reproductive health, breast/cervical cancer screenings, and pregnancies. Such experiences lower the threshold for health seeking behavior, as women are more familiar with primary care[12], which in turn promotes greater healthcare engagement and education.

DIAGNOSIS

A person's perceived gender - stemming from socially constructed gender norms - can lead to varied responses from clinicians, who may diagnose and suggest treatments differently based on gender. Gender can play a role in shaping decisions, the utilization of preventive measures, and the referral for or acceptance of various treatment strategies[13].

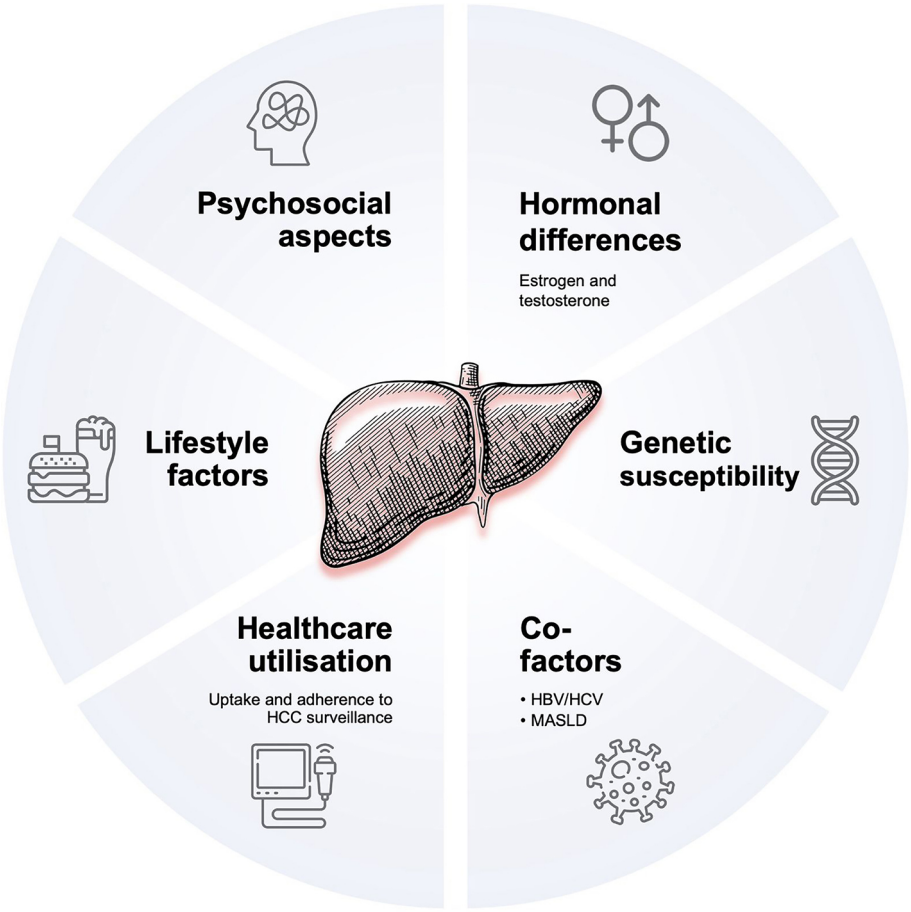

Figure 1. Factors contributing to sex differences in HCC. HCC: Hepatocellular carcinoma; MASLD: metabolic dysfunction-associated steatotic liver disease; HBV: hepatitis B virus; HCV: hepatitis C virus.

HCC prognosis remains poor largely due to late-stage presentation and diagnosis - early detection is vital in improving patient outcomes. Relative to males, females are, on average, diagnosed with HCC at an older age and are more frequently diagnosed via surveillance methods. The HCCs in females tended to be diagnosed at an earlier stage, and were typically well-differentiated, smaller, and fewer in number at the time of diagnosis[14]. The diagnosis of early-stage HCC improves survival outcomes - allowing for a higher chance for curative treatment, resulting in a better overall prognosis and lower recurrence rates.

IMPACT OF SEX HORMONES

Sex hormones have been postulated to contribute to the differences in HCC between males and females. The lower production of estradiol and a reduced response to the action of estradiol convey a greater progression of hepatic fibrosis and HCC in men and postmenopausal women, relative to premenopausal women[15]. A meta-analysis observed that the use of menopausal hormone therapy, along with increasing parity, was associated with a decreased risk of HCC. On the other hand, women who had undergone an oophorectomy were at an increased risk of HCC. These findings correlate with the degree of estrogen exposure and its resultant protective effect against HCC. Interestingly, an inverse association between menarcheal age and HCC risk was also observed. However, it is postulated that because a person's age of menarche is associated with their socioeconomic status, race/ethnicity and BMI, these confounders may be what is affecting subsequent HCC risk[16]. Interestingly, estrogen exposure resulted in greater liver injury in

male mice with the deficient *Foxa1/2* gene. The tumor-promoting effect of estrogen was observed in the absence of the *Foxa1/2* gene, suggesting that the protective effect of estrogens may be normally dominant over its hepatocarcinogenic effect[17].

A large single-center prospective study of MASLD patients also showed that postmenopausal women, as well as men, had a higher risk of having more severe fibrosis compared to premenopausal women, irrespective of the degree of background hepatocyte ballooning and portal inflammation, suggesting the protective estrogen effects on hepatic fibrosis among MASLD patients[18]. Conversely, studies have indicated that testosterone promotes cell growth and carcinogenesis, thereby increasing the risk of HCC in patients with liver cirrhosis[19]. However, the role of estrogens in the pathogenesis of HCC remains somewhat controversial and conflicting, with possible implications of aromatase-driven elevated estrogen formation and persisting signaling in liver cancer development and progression[20]. Sex hormones, and estrogens in particular, possess complex roles in liver biology and carcinogenesis, and appear to exert both stimulating and suppressive effects on the development of HCC, influenced by factors including a person's sex, co-morbids, level of exposure, and whether endogenous or exogenous in origin[19]. Carruba has postulated a mechanism for liver tissue damage and repair regulated by estrogen. In this process, liver injury triggers increased aromatase expression and activity, which boosts estrogen production. This rise in estrogen promotes the growth and differentiation of stem or progenitor cells, facilitating tissue repair and maintaining liver tissue equilibrium. However, genetic or epigenetic disruption can result in abnormal terminal differentiation of stem or progenitor cells due to excessive and uninhibited aromatase, estrogen, and subsequent amphiregulin (AREG) activation. In addition to an abnormal expansion of the liver stem cell niche, tissue damage remains unresolved. This vicious cycle of perpetual activation may contribute to the development of HCC[20]. Notably, males had higher recurrence of HCC after curative hepatectomy compared to females, where early (but not late) recurrence was more common[21] - a phenomenon the authors hypothesize is related to micro-metastasis impacted by the level of sex hormones.

Interestingly, the use of oral contraceptive pills has been linked to increased long-term survival in female patients after curative treatment of HCC[22]. Despite the long-held association between sex hormones and HCC, the use or manipulation of both estrogen[23] and testosterone[24] has not shown therapeutic benefits for HCC. Nonetheless, this remains an intriguing avenue for research.

The interaction between sex hormones and host immune function, liver cells, and HBV replication affects the course and management of HBV infection. Male and female sex hormones have been implicated in regulating HBV transcription and modulating HBV-specific immune response, thereby significantly altering their carcinogenic potential. Males with HBV were observed to have a HCC incidence five to seven times higher compared to female HBV patients. Stimulation of androgen receptors through direct binding to the androgen-responsive element sites in viral enhancer I has been linked to increased hepatitis B viral loads as a result of more pronounced HBV transcription, leading to an increased likelihood of HCC[25]. In contrast, postmenopausal women have a greater incidence of HBV-related HCC compared to premenopausal women - it has been therefore postulated that estrogens contribute to lowering HBV levels[24]. Overall, it is observed that men typically experience more rapid progression from HBV infection to HCC compared to women. In a similar vein, the male sex is an independent risk factor for accelerated progression toward liver cirrhosis in the untreated HCV cohort, whereas high estrogenic activity was found to limit the replicative activity of HCV[24].

GENETIC FACTORS

Genetic modifications modulate the effect of sex hormones in the process of hepatocarcinogenesis. The *Foxa1/2* gene appears to regulate multiple pathways in the prevention and promotion of HCC via the estrogen receptors and androgen receptors, respectively, while single nucleotide polymorphisms at *Foxa2* binding sites appear to contribute to greater HCC risk in women in particular[17].

Genetic factors have also been implicated in the disparity between the prevalence of HCC risk factors. The Patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) gene plays a crucial role in the pathogenesis of MASLD and has greater expression in women. The I148M variant of the gene is associated with increased liver fat content and disease severity. It has also been shown to be induced by estrogen receptor-α agonists[26] and, compared to men, poses a greater MASLD risk in postmenopausal women. This may be a contributory factor as to why MASLD appears to disproportionately affect women in old age.

The observation of environmentally influenced changes in heritable gene expression underscores the complex interaction between genetics and the environment. Epigenetics and metabolic reprogramming are shown to contribute to the onset and progression of MASLD-induced HCC, marking an emerging area of research[27]. The effect of co-factors of HBV and HCV infection leads to epigenetic aberrant modification of DNA methylation, leading to progression to HCC. Multiple genes, including *p16* (*INK4A*), *GSTP1*, *CDH1* (E-cadherin), *RASSF1A*, and *p21* (WAF1/CIP1), have been recognized as undergoing epigenetic alteration in HBV infection, while the *SOCS-1*, *Gadd45β*, *MGMT*, *STAT1*, and *APC* genes have been identified in HCV infection[28]. Moreover, it has been shown that HBV integration and mutations of the telomerase reverse transcriptase gene (*TERT*) promoter region were more frequent in males with HCC. *TERT* transcription had increased responsiveness to sex hormones, with enhancement by androgen receptors driving hepatocarcinogenesis, and suppression by estrogen receptors[29].

The progression and prognosis of HCC may also be influenced by genetic factors. A total of 861 sex-related molecules resulting in significant suppression of cancer-related diseases and functions were found in non-tumor liver tissues of females compared to male HCC patients. A member of the cytochrome P450 family, *CYP39A1*, with marked preferential expression seen in females, was shown to be a strong suppressant of HCC progression[30]. Y-chromosome genes, particularly the *SRY* gene, may contribute to the higher incidence and aggressiveness of HCC in men. The overexpression of *SRY* in male mice has been shown to promote hepatocarcinogenesis. In contrast, the long non-coding RNA *FTX* gene, located on the X chromosome, acts as a tumor suppressor with higher expression in women, providing a protective effect against HCC[24].

BEHAVIORAL RISK FACTORS

Men have historically been more prone to exposure to HCC risk factors, which has contributed to the significant disparity in HCC prevalence. Activities that improve male bonding and are attributed to masculinity, such as intravenous drug use, alcohol misuse, and cigarette smoking[24], may explain the male predominance in these HCC risk factors. However, lifestyle and behavioral trends have been evolving with time. There has been a substantial rise in risk-related behaviors in females observed over recent decades[2]. Interestingly, the improvement in mortality rates in the younger adult cohort was more marked in young men, who saw a greater reduction in HCC mortality compared to their female counterparts[31]. This evolving trend should be closely monitored in the future, and is likely attributed to the disproportionate relative increase in the burden of MASLD, metabolic risk factors, and alcohol consumption in women. There appears to be a diminishing disparity in alcohol consumption between the sexes, with evidence pointing to an increase in alcohol use among women, while men have not shown a similar trend. Moreover, females

also appear more susceptible to alcohol-induced liver inflammation than males, resulting in a more rapid progression to fibrosis and, consequently, HCC[32], which is explained by differences in ethanol metabolism between the sexes.

Metabolic syndrome and obesity are worrying public health issues - their rapidly rising prevalence over the decades coinciding with the increasing incidence of HCC. The presence of diabetes/prediabetes in MASLD patients was an independent predictor of greater severity of liver fibrosis[18] and, thus, HCC risk. Uncomplicated steatosis, MASH fibrosis, and resultant HCC are more common in men[33]. Compared to females, inflammatory adipokines from visceral adiposity, resulting in chronic hepatocyte inflammation, appear to preferentially increase the risk of liver fibrosis in males and expedite the eventual progression to liver cirrhosis[2]. Studies have identified multiple mechanistic differences in MASLD-related HCC, with males being more susceptible to elevated hepatic metabolic stress. In mouse model studies, male mice exhibited a higher risk of oxidative DNA damage, a stronger immune response from IL-6 stimulation, and reduced levels of tumor suppressor microRNA in the liver, associated with distinct microbiota. These factors collectively contribute to an increased risk of HCC in male mice[34].

Notably, while the risk of developing MASLD and MASH is higher in men[2], obesity is more frequently observed in females, with up to 38% of US women being affected currently. As women transition through menopause with advancing age, they lose protective factors previously afforded by sex hormones[33], leading to an increased likelihood of MASLD/MASH in those over 60[2]. This is contributed by the decrease in physical activity with age, metabolic and hormonal changes with resultant alterations in fat metabolism and an increase in visceral adipose tissue. A multi-center prospective study, mostly comprising male participants, found that HCC in MASLD patients, compared to those with HCV, were likely to display a more infiltrative pattern of greater volume, and was more often identified outside scheduled intervals, with cirrhosis present in only half of all MASLD-HCC patients[35].

Understanding the clinical course of different etiologies of HCC, in relation to males and females of various age groups, especially in the context of MASLD, which is likely to represent a significant burden of future HCC, will be vital in developing more effective age- and sex-specific public health screening and interventions.

OUTCOMES AND SURVIVAL

Although it is well-documented that being male increases the risk of developing HCC, there is still conflicting evidence as to whether being female influences survival outcomes[14,36]. The variation in HCC progression and outcomes between the different sexes is more pronounced in the younger population cohorts. Despite a better overall survival seen in women < 65 years compared to men, similar overall survival was seen in both sexes over 65 years old[23]. This observation highlights the likely enhanced protective influence of female hormones before menopause[26], potentially influencing the onset, development, and outcomes of HCC. Differences in the course and prognosis of HCC are most marked between the sexes in younger age groups - this is where targeted population intervention will likely yield the most benefit.

In a large retrospective study in the US, primarily involving racial and ethnic minorities and including only a small percentage of HBV patients, women with HCC were shown to have reduced mortality and higher overall survival compared to men, even after accounting for demographic variations of race, ethnicity, and age. Female sex was also independently associated with both earlier HCC detection and improved outcomes following the first HCC treatment[37]. On the contrary, another cohort study of predominately Asian patients

with HCV and HBV showed that females were not associated with increased survival, despite reduced HCC burden and a more advanced age at the time of diagnosis[36].

Innate and adaptive immune responses differ between the sexes - for instance, estrogen-driven suppression of IL-6 expression has been associated with a decreased risk of HCC. Yet, these sex-specific differences in immune system regulation may also influence immunotherapy efficacy. Interestingly, a meta-analysis of five phase III trials indicated that women showed a reduced overall survival benefit from immune checkpoint inhibitor (ICI) treatment for advanced HCC compared to men, potentially due to lower immunogenicity of HCC tumors in females[38]. Further studies are needed to study sex-specific responsiveness to ICIs.

These conflicting results highlight the challenges of trying to isolate sex as a risk factor in a very heterogeneous population. The differences observed may be attributed to contrasting cohort demographics and socioeconomic factors, underlying HCC etiology, and the inherent limitations of a retrospective analysis. More prospective studies looking at HCC, with greater analysis of reproductive status and history including both oral contraceptive use and hormonal therapy, may yield greater insight into this important variable.

PSYCHO-SOCIOECONOMIC ASPECTS

Notably, despite the disproportionately higher number of female patients with an earlier and less advanced diagnosis of HCC compared to males, the number of females and males undergoing liver transplantation (LT) and curative resection remained similar in one study[36]. This may point toward an underlying disparity between how men and women with HCC are being treated, or their respective uptake of offered treatments.

Although there is no specific literature regarding sex-related treatment disparities in HCC, societal biases and cultural norms can influence the decisions of healthcare providers. For example, single patients were less likely to be offered potentially life-saving surgery or radiotherapy due to the perceived lack of social support[39]. Advanced-age, female, nonwhite, and unmarried cancer patients were also less likely to receive aggressive care near the end of life[40].

Conscious or unconscious bias may lead to differences in treatment recommendations, with males perceived as better able to undergo or tolerate more aggressive treatment options compared to females. This possible sex bias has been observed in disparities in the treatment of other types of cancers - for example, older females with gastroesophageal cancer were less frequently allocated to curative treatment compared to males[41], and also received systemic treatment less often in palliative cases[42].

Cultural expectations about gender roles can affect access to healthcare and uptake of treatment. Women may face greater barriers to accessing healthcare due to lower socioeconomic status, as well as caregiving responsibilities, or cultural beliefs about their health needs being secondary to others[43]. Responsibility for housework and feminine personality traits have been associated with poorer access to and uptake of healthcare[12].

Higher HCC incidence, more distant spread at diagnosis, and a poorer 5-year survival were observed among the low-socioeconomic-status groups in nearly all races/ethnicities[44]. It is important to note that the health-related consequences of sex inequality particularly affect poor women, who are often over-represented in low-paying jobs[45]. Conversely, patients with a higher level of education were more likely to accept and adhere to screening and treatment, while less-educated patients tended to live in an environment with increased exposure to HCC risk factors, and also had a lower probability of getting married[45].

Interestingly, marriage has been shown to be an independent prognostic factor for survival in HCC[43], attributed to spousal emotional and social support.

Geographic characteristics also appear to play a role in the survival of HCC patients. In one study, despite living in the most socioeconomically depressed neighborhoods, median survival was longest in Hispanics, who tended to live closest to any transplant or academic cancer center[46].

LT

Though HCC treatment has taken a big leap, LT is still the curative therapy of choice for people with HCC in an ideal setting. However, several studies have shown evidence of sex disparities in the realm of LT in general, particularly in terms of access, receipt of transplant, outcomes, and mortality[47,48]. A recent study evaluated 81,357 adults waitlisted for a liver transplant and found women had an 8.6% greater risk of mortality while awaiting a liver transplant compared to men. In addition, it showed that women were 14.4% less likely to receive a deceased donor liver transplant[30]. One of the contributory factors raised for this disparity involves concerns with potential inaccuracies in prioritizing patients for liver transplant solely with the model for end-stage liver disease (MELD) score, given the sex-based differences in serum creatinine levels[49-51]. Another factor includes anthropometric and liver measurements resulting in women being more likely to have donor livers declined due to donor-recipient size mismatch[52].

Among LT candidates with HCC, MASH has become the fastest-growing etiology in both women and men, surpassing chronic HCV to become the leading cause of liver disease in both male and female patients with HCC on the waitlist[53,54]. A recently published updated study looked at sex-based disparities using registry data from the United Network for Organ Sharing database among LT candidates with HCC on the waitlist from 2000 to 2022. Compared to male patients, female patients spent a significantly longer time on the waitlist and had a lower likelihood of LT receipt. Interestingly, posttransplant mortality in MASH-related HCC was lower in female patients compared to male patients[53]. The evidence of sex disparities in LT in general, as well as in the subgroup of patients with HCC, highlights a need for better strategies to ensure equity. The evolution of the traditional MELD score to MELD 3.0 may be a start to closing the disparity in sexes, particularly for candidates on the LT waitlist[55].

CONCLUSION AND FUTURE PERSPECTIVES

Although the disparity in HCC between males and females is a well-documented phenomenon, the impact of sex on HCC pathophysiology remains overlooked and underemphasized in clinical practice today. As a fundamental aspect of precision medicine, sex differences should be integrated into everyday decision making. There is a pressing need to transition from a one-size-fits-all approach to a more individualized and holistic strategy aiming to promote sex equity in healthcare[13].

Additional research is warranted to investigate mechanisms underlying these clear sex differences, specific to various age groups, in the pathogenesis and prognosis of HCC. This may guide public health strategies in addressing sex-specific risks, and enable more effective early detection and screening protocols targeting earlier diagnosis in higher-risk populations. Moreover, a greater understanding of the association between sex hormones and HCC may help enhance risk assessment and prevention strategies in specific cohorts, and guide reproductive health considerations and management of hormone-related therapies. Sex differences in HCC tumor biology suggest that HCC may lead to differing therapeutic efficacy between males and females[31]. A greater understanding may contribute to the development of targeted therapies that specifically address hormonal pathways, and studying how sex hormones alter therapeutic efficacy response and patient outcomes is important for refining HCC treatment approaches. In conclusion, further research

on these fronts could not only clarify the reasons behind this disparity in HCC, but also lead to more effective, personalized prevention and treatment strategies, ultimately improving patient outcomes and closing the gap across both sexes.

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Authors' contributions

Made substantial contributions to the conception, design, drafting, and revision of this manuscript: Ho JKH, Thurairajah PH, Leo J, Huang DQY, Fan KH

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Huang DQY is on the advisory board of Roche and Gilead, while the other authors have declared that they have no conflicts of interest.

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