

# Nonalcoholic steatohepatitis-related hepatocellular carcinoma: is there a role for the androgen receptor pathway?

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**Abstract:** The epidemic of insulin resistance, obesity, and metabolic syndrome has led to the emergence of nonalcoholic steatohepatitis (NASH) as the most common cause of liver disease in the US. Patients with NASH are at an increased risk for hepatic disease-related morbidity and death, and chronic inflammation in NASH patients can lead to hepatocellular carcinoma (HCC). The prevalence of HCC is higher in males than in females, and genetic studies have identified androgen and androgen receptors (ARs) as partially responsible for the gender disparity in the development of liver disease and HCC. Although many factors are known to play important roles in the progression of inflammation in NASH patients, the role of androgen and AR in the progression of NASH to HCC has been understudied. This review summarizes the evidence for a potential role of androgen and the AR pathway in the development of NASH-related HCC and in the treatment of HCC. It has been proposed that AR plays a role in the progression of HCC: inhibitory roles in early stages of hepatocarcinogenesis and tumor-promoting roles in advanced stages. AR can be activated by several pathways, even in the absence of androgen. While AR has been explored as a potential therapeutic target in HCC, several clinical trials have failed to demonstrate a clinical benefit of antiandrogen drugs in HCC. This review discusses the potential reason for these observations and discuss the potential future trials design in this important setting.

**Keywords:** hepatocellular carcinoma, nonalcoholic steatohepatitis, androgen receptor, flutamide, sorafenib

## Introduction

Hepatocellular carcinoma (HCC) is an aggressive neoplasm with a poor prognosis, resulting in a 5-year relative survival rate of only 17.2% and an estimated 24,550 deaths in the US in 2015.<sup>1</sup> Over the last three decades, the incidence of HCC in the US has increased from 1.4 per 100,000 to 8.2 per 100,000 per year.<sup>2</sup> The incidence of HCC is higher in developing countries, particularly those in the Asian Pacific regions, owing to the high prevalence of chronic hepatitis B and C viral infections. However, the incidence in developed countries has also been increasing owing to the emergence of nonalcoholic steatohepatitis (NASH) as an important risk factor.<sup>3,4</sup> In fact, recently, a large retrospective study demonstrated that the proportion of non-virus-related HCC increased from 10% in 1991 to 24.1% in 2010, with most cases related to nonalcoholic fatty liver disease (NAFLD) and diabetes.<sup>5-7</sup> In a Japanese study, the 5-year HCC development rates in cirrhosis patients were 11.3% in NAFLD cirrhosis, 12.5% in alcoholic cirrhosis, and 30.5% in hepatitis C virus cirrhosis, showing similar rates of HCC development in both alcoholic and NAFLD-related cirrhosis.<sup>8</sup>

Although metabolic syndrome had the lowest relative risk among other factors for HCC (1.5%–2.5%), its high prevalence in the general population (30%–40%) led to the highest population-attributable fraction.<sup>9</sup>

Regardless of the underlying etiology, the incidence of HCC is higher in males, with male-to-female ratios varying between 3:1 and 4:1 depending on geographic location.<sup>10,11</sup> Moreover, males have poorer survival despite there being many treatment options.<sup>12–14</sup> The increased incidence and disease aggressiveness in males suggest that androgen and androgen receptors (ARs) might promote HCC development and progression and/or that estrogen and estrogen receptors might suppress HCC development.<sup>15</sup> This review summarizes the evidence for the potential role of androgen and ARs in NAFLD/NASH-related HCC.

## NAFLD pathogenesis

NAFLD is the most common cause of liver dysfunction, with a prevalence of 20%–30% in the general population and up to 57%–74% among obese patients.<sup>16</sup> NAFLD was usually considered to be one of the components of the metabolic syndrome and to be strongly linked to central obesity, insulin resistance, dyslipidemia, and hypertension (Table 1).<sup>17–22</sup> Recent studies support the association of NAFLD with type 2 diabetes mellitus or metabolic syndrome, suggesting that NAFLD actually precedes the development of both conditions and is considered as a risk factor for development of type 2 diabetes mellitus.<sup>23</sup> NAFLD includes disorders ranging from isolated liver steatosis (in which triglycerides

accumulate in the hepatocytes), characterized by macrovesicular fatty change with or without nonspecific inflammation in the absence of cellular injury (ballooning), to NASH (characterized by the presence of additional cellular ballooning) and, subsequently, to cirrhosis and even HCC.<sup>24–26</sup> Fibrosis is the most important determinant of the outcome.

The molecular pathogenesis of liver steatosis and its progression to cirrhosis and eventually HCC is not clearly understood. Previously, a two-hit theory had been proposed to explain the molecular changes through which fatty liver leads to lipid peroxidation, cytokine production, and Fas ligand induction.<sup>27</sup> However, more recently, a multiple-hit theory which better explains NAFLD development and progression to HCC has gained ground. The first hit is caused by insulin resistance and leads to fat accumulation in the hepatocytes, induced by both lipolysis and hyperinsulinemia. This is followed by multiple hits with many factors playing different roles, including genetic predisposition, obesity, oxidative stress and mitochondrial dysfunction, inflammation, adipokines, small intestinal microbacteria, and others. Hyperinsulinemia could also lead to increased levels of insulin growth factor-1, which causes stimulation of insulin growth factor receptors and promotion of proliferative and antiapoptotic effects, and vascular endothelial growth factor-mediated promotion of angiogenesis.<sup>28</sup>

Thus, in this setting, the liver is more susceptible to oxidative stress and inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), which promote progression to NASH and fibrosis. IL-6 activates signal

**Table 1** Five parameters of the metabolic syndrome according to the WHO and AACE

Parameter	WHO (1998)	IDF (2005)	EGIR (1999)	NCEP-ATP III	ATP III (2001)	AHA/NHLBI (2005)
Required for diagnosis	Insulin resistance	Ethnicity-based increased waist circumference	Insulin resistance	–	Any three out of five	Any three out of five
+ Number of abnormalities	$\geq 2$	$\geq 2$	$\geq 2$	$\geq 3$	–	–
Glucose	DM	$\geq 100$ mg/dL	DM	$\geq 100$ mg/dL	$\geq 110$ mg/dL	$\geq 100$ mg/dL
HDL cholesterol	Males $<35$ mg/dL, females $<39$ mg/dL	Males $<40$ mg/dL, females $<50$ mg/dL	Males and females $>39$ mg/dL	Males $<40$ mg/dL, females $<50$ mg/dL	Males $<40$ mg/dL, females $<50$ mg/dL	Males $<40$ mg/dL, females $<50$ mg/dL
Triglycerides	$\geq 150$ mg/dL	$\geq 150$ mg/dL	$\geq 150$ mg/dL	$\geq 150$ mg/dL	$\geq 150$ mg/L	$\geq 150$ mg/L
Obesity	Waist/hip $>0.9$ (males) or $>0.85$ (females); BMI $\geq 30$ kg/m <sup>2</sup>	WC: males $\geq 102$ cm, females $\geq 88$ cm	WC: males $\geq 94$ cm, females $\geq 80$ cm	WC $\geq 94$ cm	WC: males $\geq 102$ cm, females $\geq 88$ cm	WC: males $\geq 102$ cm, females $\geq 88$ cm
Hypertension	$\geq 140/90$ mmHg or use of antihypertensive drugs	$\geq 130/85$ mmHg or use of antihypertensive drugs	$\geq 140/90$ mmHg or use of antihypertensive drugs	$\geq 130/85$ mmHg or use of antihypertensive drugs	$\geq 130/85$ mmHg or use of antihypertensive drugs	$>130/85$ mmHg or use of antihypertensive drugs

**Abbreviations:** AACE, American Association of Clinical Endocrinologists; BMI, body mass index; DM, diabetes mellitus; HDL, high density lipoprotein; WC, waist circumference; WHO, World Health Organization; IDF, International Diabetes Federation; EGIR, European Group for the Study of Insulin Resistance; NCEP-ATPIII, National Cholesterol Education Program Adult Treatment Panel III; ATP III, Adult Treatment Panel III.

transducer and activator of transcription 3, which induces cell proliferation and antiapoptotic mechanisms. TNF- $\alpha$  activates pro-oncogenic pathways, including c-Jun N-terminal kinase, nuclear factor kappa-light-chain-enhancer of activated B cells, mammalian target of rapamycin, and the extracellular signal-regulated kinases.<sup>29-32</sup> Interestingly, several studies indicated that both dietary and genetic obesity could promote liver inflammation and tumorigenesis by enhancing IL-6 and TNF- $\alpha$  expression.<sup>33-36</sup>

Finally, the high circulating levels of leptin in NAFLD have been recently shown to exert proinflammatory and profibrogenic effects.<sup>37,38</sup> In addition, there is evidence that lipid peroxides and free radicals are elevated in metabolic syndrome; these may cause oxidative injury, endoplasmic reticulum stress, mitochondrial dysfunction, and apoptosis.<sup>15</sup>

### Role of gender differences in NAFLD

Several studies have shown that gender differences play a role in various liver disorders. Earlier beliefs that NAFLD/NASH was a female-predominant condition have been dispelled; recent studies have shown higher prevalence in males.<sup>39-46</sup> Interestingly, in a preclinical study, a high-fat, high-cholesterol diet induced NASH and hepatic ballooning in ovariectomized mice, which showed that estrogen deficiency promoted NASH progression, while estrogen treatment reversed it.<sup>47</sup> Furthermore, many studies have shown that NAFLD patients have significantly lower levels of sex hormone binding globulin, a glycoprotein that binds to sex hormones (both estrogen and androgen).<sup>48,49</sup> Increased prevalence of NAFLD has also been reported in patients with polycystic ovary syndrome (PCOS).<sup>50,51</sup> Diethylnitrosamine administration caused greater increase in serum IL-6 in male than in female mice. Also, ablation of IL-6 abolished the gender differences in hepatocarcinogenesis in mice.<sup>52,53</sup>

However, the roles of androgen in the development of NAFLD remain unclear, as the results of experimental and clinical studies have been inconsistent.<sup>54,55</sup> For example, Jones et al found a significantly higher degree of hepatic steatosis in high-androgen-expressed PCOS patients as compared to low-androgen-expressed PCOS patients or controls.<sup>56</sup> Another study observed that androgenic steroid usage by bodybuilders could be a possible risk factor for NAFLD.<sup>57</sup> In contrast, Haider et al showed that normalizing serum testosterone levels in obese hypogonadal males could improve their weight loss and metabolic state and suppress the development of NASH.<sup>58</sup>

The role of ARs in the pathogenesis of NAFLD is also unclear. An experimental study showed that whole-body

AR-knockout mice fed a high-fat diet developed liver steatosis and insulin resistance, possibly through either 1) suppression of fatty acid synthesis by decreased sterol regulatory element-binding protein 1 (SREBP1) expression or 2) increased insulin sensitivity by suppression of phosphoenolpyruvate carboxykinase and protein tyrosine phosphatase 1B.<sup>59</sup> Notably, other studies showed that activation of AR in orchidectomized mice led to obesity and altered lipid metabolism, and progression of NASH to HCC.<sup>60</sup> This may have been mediated either through downregulation of liver X receptor (which complements SREBP2 activation and increases cellular cholesterol levels) or through upregulation of AR messenger RNA levels and increased activity of CYP27A1 (an enzyme that plays a significant role in cholesterol homeostasis and vitamin D3 metabolism through activation of the c-Jun N-terminal kinase pathway).<sup>61,62</sup>

### Prevention of NASH/metabolic syndrome-related HCC using existing drugs

Statins (3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors) are commonly prescribed for prevention of cardiovascular disease and act by decreasing the biosynthesis of cholesterol. Statins may play a role in the prevention of cancer development by inducing apoptosis and inhibiting cellular proliferation, angiogenesis, inflammation, and immunomodulation.<sup>63</sup> In multiple observational studies,<sup>64-67</sup> the use of statins has been associated with a decreased risk of HCC in patients with viral hepatitis and those with diabetes, and statins may also decrease the risk of HCC recurrence after surgical treatment.<sup>68</sup> However, a randomized controlled trial did not demonstrate a significant difference in HCC incidence between the statin and placebo groups.<sup>69</sup>

In diabetic patients, the use of both metformin and thiazolidinediones (peroxisome proliferator-activated receptor gamma agonists) was associated with a decreased cancer risk, whereas sulfonylurea was correlated with an increased overall risk of cancer.<sup>70</sup> Also, the use of combined statin and metformin in diabetic patients showed no benefit to reduce the risk of HCC in Asian population.<sup>71</sup> Metformin has been shown to inhibit hepatocellular proliferation and leads to arrest of the cell cycle at the G0/G1 phase by downregulation of cyclin D1,<sup>72</sup> while thiazolidinediones were reported to decrease the risk of HCC by accumulation of p27, inhibition of ubiquitin-proteasome, MEK-ERK signaling, and induction of apoptosis.<sup>70,73,74</sup> Also, drugs of proven antifibrogenic efficacy may potentially decrease the risk of developing HCC.<sup>75</sup>

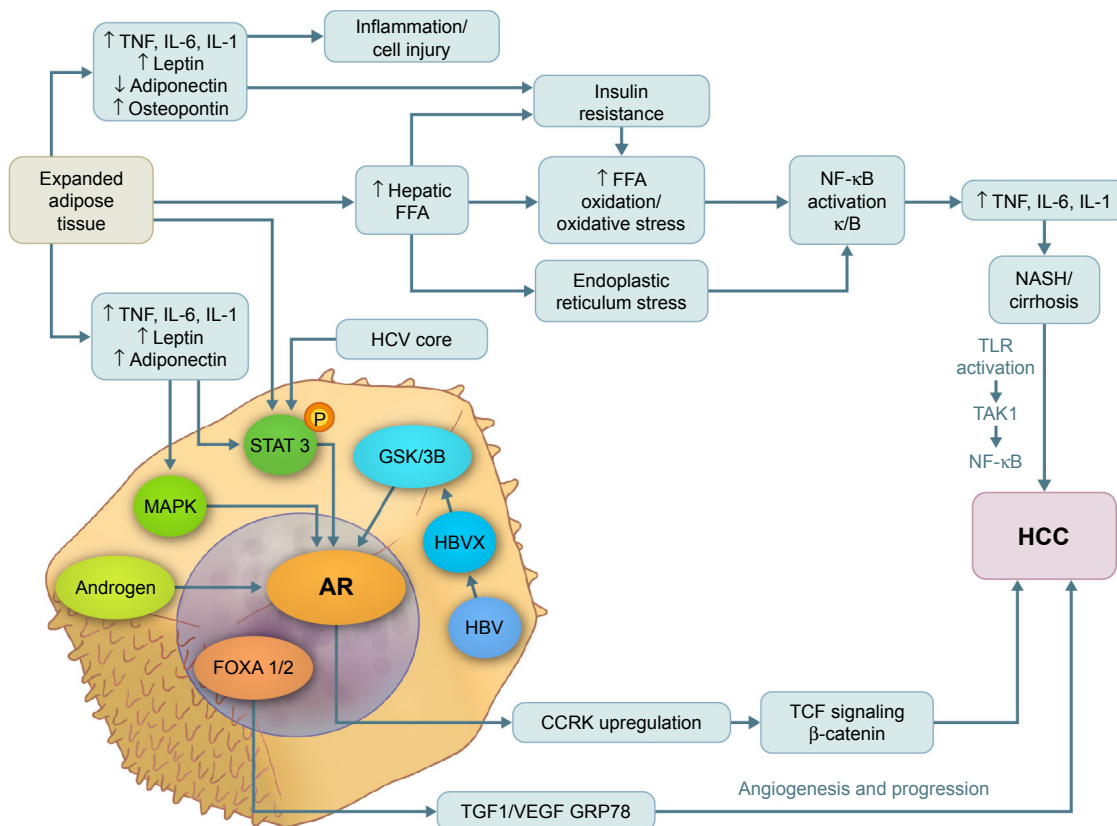
## Mechanistic pathway of androgen and ARs in hepatocarcinogenesis

Both estrogen and androgen are steroid hormones that mediate their action by binding to nuclear receptors and acting as transcription factors to regulate the expression of multiple genes. Progression from hyperplasia to HCC is associated with suppression of estrogen receptors and elevated AR expression.<sup>76–80</sup> In addition, several studies<sup>81</sup> have shown that AR messenger RNA protein is expressed at higher levels in hepatic tumor tissue than in normal hepatic tissue. The *AR* gene is located on the X chromosome with a single copy in males. The AR molecule is a ligand-activated transcriptional factor with three domains – the N-terminal domain, the DNA-binding domain, and the ligand-binding domain.<sup>82</sup> ARs can be activated directly by androgen, inducing cell cycle-related kinase (CCRK) transcription through promoter binding; CCRK then upregulates  $\beta$ -catenin/T-cell factor signaling, leading to promotion of hepatocarcinogenesis.<sup>83</sup> ARs can also be activated directly in the absence of androgen by many alternative pathways

such as the mitogen-activated protein kinase, AKt, and signal transducer and activator of transcription pathways, which are also involved in hepatocarcinogenesis (Figure 1).<sup>84,85</sup> In an experimental study, adding functional ARs to HCC cells promoted cell growth and increased cellular oxidative stress, DNA damage, and suppression of the p53-mediated sensing/repairing system and of cell apoptosis.<sup>86</sup> Furthermore, several studies have shown that AR is expressed in both normal liver and malignant tissues, but at higher levels in HCC tumor tissue.<sup>56,61,86</sup>

## Clinical evidence of androgen’s role in promoting HCC recurrence and metastasis

Several clinical studies have reported a strong correlation between AR expression and the rate of HCC recurrence (summarized in Table 2).<sup>87–89</sup> However, there is controversy regarding the relationship between AR and tumor characteristics such as size, another factor that affects tumor recurrence.<sup>57,70</sup>



**Figure 1** Pathways of androgen and AR in the pathogenesis of NASH, cirrhosis, and hepatocellular carcinoma.

**Note:** Visual Art: © 2015 The University of Texas MD Anderson Cancer Center.

**Abbreviations:** AR, androgen receptor; CCRK, cycle cycle-related kinase; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IL, interleukin; MAPK, mitogen-activated protein kinase; NASH, nonalcoholic steatohepatitis; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; STAT 3, signal transducer and activator of transcription 3; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; GSK3b, glycogen synthase kinase 3 beta; FFA, free fatty acid; HBVX, hepatitis B virus protein X; TGF1, tumor growth factor 1.

**Table 2** Clinical studies that evaluated the role of androgen and its receptors in the recurrence of surgically treated HCC

Author	Year	Country	Sample size	HCC risk factor	Sex (M/F)	AR expression	Recurrence rate	Survival rate
Nagasue et al <sup>87</sup>	1989	Japan	45	Alcoholic	15	31 AR+ (25 M/4 F)	AR+ 67.9%	AR+ 1 year: 84%; 5 years: 17.3% AR- 1 year: 100%; 5 years: 62.2%
				HBsAg	24	14 AR- (6 M/8 F)	AR- 33.3%	
				AntiHbc	32			
Boix et al <sup>88</sup>	1995	Spain	43	Cirrhosis	40	30 AR+	AR+ 1 year: 34%; 2 years: 51%	Not reported
				AntiHBs	15	13 AR-	AR- 1 year: 0%; 2 years: 20%	
				Normal	3			

**Abbreviations:** AntiHbc, Anti Hepatitis B core antibodies; antiHBs, antihepatitis B surface antibodies; AR, androgen receptor; F, female; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; M, male.

Moreover, the role of AR in promoting metastasis in HCC has been understudied. A few studies have reported a role for AR in metastatic HCC lesions, which may include the following: 1) AR activation by its ligand leads to increased expression of *IDI* (a metastasis-promoting gene), which causes HCC cell migration and invasion<sup>90</sup> or 2) tighter and faster adhesion of the cancer cells to collagen IV and various extracellular membranes occurs through  $\beta$ 1 integrin expression induced by activated ARs.<sup>91</sup> The latter effect of AR on cell adhesion was shown to be mediated by the  $\beta$ 1 integrin-phosphoinositide-3-kinase (PI3K)/Akt pathway. In contrast, another study found that AR expression was significantly reduced in advanced metastatic lesions compared with early primary HCC lesions, with the AR upregulated in tumors <3 cm.<sup>92</sup>

### Effect of antiandrogen treatment on HCC outcome

Despite the mounting evidence suggesting the potential role of the AR pathway as a therapeutic target in HCC, data on the use of antiandrogens are limited to a few clinical trials and no definite activity has been reported using this strategy (Table 3).<sup>87,93–99</sup> One reason for the failure of these clinical trials could be the fact that these studies included mostly advanced and metastatic HCC patients, and the role of AR in late-stage HCC – whether it promotes or suppresses invasion and metastasis – remains unclear. Also, AR expression might be more critical than androgen concentration in HCC<sup>92</sup> and no correlative studies have tested the predictive value of expression of AR in the tissue of HCC patients. Finally, most trials were performed on viral hepatitis-induced HCC, which may not have the same histologic characteristics or pathogenesis as non-hepatitis-induced HCC. The biological heterogeneity of HCC makes the prognosis of tumor growth, survival of patients, and treatment outcomes difficult.<sup>100–102</sup>

### Current systemic therapy in HCC: potential role of AR

Currently, single-agent sorafenib, a putative multitargeted kinase inhibitor, is the only systemic therapy approved by the US Food and Drug Administration to treat patients with advanced HCC. Sorafenib prolongs the overall survival by approximately 3 months in this population<sup>13</sup> Phase II studies of other targeted drugs such as sunitinib, linifanib, erlotinib, ramucirumab, and everolimus demonstrated promising results in the management of late-stage HCC, but Phase III studies of these agents did not show overall survival benefit in unselected patient populations.<sup>103–105</sup> Notably, subgroup analyses of the Sorafenib HCC Assessment Randomized Protocol (SHARP) trial suggested that survival outcomes varied with patient demographics, geographic location, and risk factors. Interestingly, recent Phase II studies of other agents, including two studies in the first-line treatment setting conducted by the group using the combination of bevacizumab and erlotinib, showed activity in HCC,<sup>103,106–111</sup> which also suggested differential outcomes based on patients' demographics, geographic locations, and risk factors.

Another important factor that affects the outcome in HCC patient population is their tolerance to therapies, given the coexistence of HCC tumors and underlying liver disease in most of the cases. Although the adverse effects of targeted therapy are usually tolerable, serious complications can develop, especially with higher doses or in combination with another angiogenic agent or with chemotherapy. Fatigue, diarrhea, and hand/foot skin reaction are the most common dose-limiting side effects, with bleeding, arterial thromboembolism, and other fatal complications also possible.<sup>13</sup> Therefore, increasing the efficiency of sorafenib and other targeted therapies by combination with other drugs that increase their efficacy while maintaining a lower dose is essential.

**Table 3** Clinical studies that evaluated the role of antiandrogen drugs in the treatment of HCC

Author	Year	Country	Sample size (N)	HCC risk factor	Sex (M/F)	Antiandrogen type	Stage of disease	Changes in testosterone level	Overall survival rate	Responses
Forbes et al <sup>93</sup>	1987	UK	25	Alcohol 10 HBV 8 Cryptogenic 3 PBC 3 Autoimmune 1	23/2	Cyproterone acetate	Unresectable (five metastatic)	↓	3 months	3 (12%)
Gupta et al <sup>94</sup>	1988	USA	8	Alcohol 7	7/1	Ketoconazole	Unresectable	↓	Not significant	NR
Nagasue et al <sup>87</sup>	1989	Japan	16	NR	16/0	Cyproterone acetate	Unresectable/recurrent	–	Not significant	3 (19%)
Chao et al <sup>95</sup>	1996	People's Republic of China	32	Alcohol 1 Hepatitis 28 Cryptogenic 3	31/1	Flutamide	Unresectable		<3 months	NR
Grimaldi et al <sup>96</sup>	1998	France	238	Alcohol 89	202/35	Nilutamide versus placebo	Unresectable		Nilutamide 3.9 versus 5.5 months	NR
Manesis et al <sup>97</sup>	1995	Greece	85	HBV 46 Hemochromatosis 10 Other 12 Missing 37 Alcohol 21	66/19	Triptorelin versus placebo Tamoxifen + triptorelin versus flutamide + triptorelin versus placebo	Unresectable	↓	Triptorelin 3.4 versus 5.5 months 4, 3, and 4 months, respectively	NR
GRETCH <sup>98</sup>	2004	France	375	HBV 53 HCV 11 HDV 10 Alcohol 242 HCV 54 HBV 23 Other 15	375/0	Leuprorelin + flutamide + tamoxifen versus tamoxifen	Unresectable	↓	135.5 and 176 days, respectively	Not significant

**Note:** ↓ represents decrease in testosterone level.

**Abbreviations:** HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; NR, not reported; PBC, primary biliary cirrhosis.

AR was found to suppress HCC metastasis by modulating p38. Also, the addition of functional AR in SKhep1 and HepG2 HCC cells was found to decrease p38, leading to enhanced effectiveness of sorafenib against HCC cells.<sup>92</sup> In preclinical studies, sorafenib treatment had greater anti-metastatic effects against AR-positive than AR-negative HCC (66.7% vs 0%, respectively;  $P=0.0109$ ). Another study showed that sorafenib with or without AR inhibitors induced significant apoptosis in HCC cells with knocked out AR when compared with unmanipulated HCC cells; the authors concluded that inhibition of AR in combination with sorafenib may be beneficial for the treatment of HCC.<sup>90,111</sup> These data suggest that AR may be a target of combination therapy, and that AR expression may be a potential biomarker of response to sorafenib in HCC.

## Conclusion

Androgen and ARs may play a critical role in hepatocarcinogenesis and could mediate, in part, the mechanisms responsible for the gender disparity in HCC incidence. ARs can be activated both by androgen and, in the absence of androgen, by alternative pathways. Liver steatosis can progress into NASH, which can lead to cirrhosis and HCC. The high prevalence of NASH in the general population led to recent significant increase in incidence of NASH-related HCC cases. Gender disparity appears to play a significant role in the development of NASH, as NASH is more common in males than in females and also contributes to higher risk of HCC development. Nevertheless, the clinical trials conducted so far have failed to demonstrate a significant benefit of antiandrogen drugs in the treatment of HCC patients. This failure could be explained, at least partially, by 1) the marked heterogeneity of HCC, with most trials performed on virus-induced HCC; 2) the dual, yet opposite effects of AR during early and late HCC, with most trials performed on advanced HCC only; and 3) the direct stimulation of AR by pathways other than androgen. Therefore, it is critical to understand the molecular mechanisms associated with HCC in males with NASH to design successful targeted therapy studies focusing on AR pathway.

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