Effects of Statins on the Risk of Hepatocellular Carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is one of the leading causes of cancer morbidity and mortality worldwide and is one of the few cancers that is increasing in incidence. This cancer often arises in the setting of hepatic cirrhosis; however, it can also occur in patients with chronic hepatitis B virus infection without cirrhosis. Statins have been used for many years for the prevention and treatment of cardiovascular disease. Based on recent meta-analyses, these lipid-lowering agents are now being investigated for a class effect observed in the prevention of carcinogenesis. There are robust data suggesting that statins can alter biochemical pathways involved in tumorigenesis and cell survival and, thus, have a protective effect by reducing the risk of development of several types of cancer. In recent years, several studies have demonstrated that statins also can specifically decrease the risk of HCC development. Because statins are underutilized in patients with preexisting liver disease, understanding the role of statins in the prevention of HCC is important, and changes in practice guidelines supporting the use of statins as chemoprotective agents may be warranted.

Hepatocellular carcinoma (HCC) often occurs in the setting of prior liver disease, such as in patients with hepatic cirrhosis and in chronic viral hepatitis. This cancer is frequently diagnosed in advanced stages. Affected patients have a median survival of 6 to 20 months.[1] HCC results in 250,000 to 1,000,000 deaths per year and is the fifth and seventh most common cause of cancer worldwide in men and women, respectively. Additionally, large racial and ethnic disparities exist in both the incidence and clinical outcomes of HCC in the United States.[2] HCC is the second most common cause of cancer-related death in men and the sixth in women.[3] Known risk factors for HCC include hepatitis B virus (HBV) carrier state, chronic hepatitis C virus (HCV) infection, hereditary hemochromatosis, stage 4 primary biliary cirrhosis, alpha-1 antitrypsin deficiency, and cirrhosis of any etiology, including alcoholic hepatitis and nonalcoholic fatty liver disease (NAFLD).[4]

In the United States, the incidence of HCC increased more than 2-fold from 1985 to 2002. Although approximately half of this increase can be attributed to patients with chronic HCV infection, a significant portion of patients (>15%) have no clear viral or alcoholic etiology. NAFLD, obesity, and diabetes mellitus also may be important contributors to this increase in HCC.[5] Interestingly, chronic HBV infection is strongly associated with the development of this malignancy, and HCC can develop in infected patients even if there are no signs of liver cirrhosis. Regardless of this observation, the majority of patients with HBV infection in whom HCC develops have evidence of cirrhosis.[6] Other factors that increase the risk of development of HCC in patients with chronic HBV infection include viral load and the presence of hepatitis B surface antigen, indicating that active replication may drive tumor development.

Chronic HCV infection is also associated with HCC; however, affected patients almost exclusively have evidence of advanced liver fibrosis and cirrhosis. It is believed that HCC occurs in HCV-infected patients due to the rapid turnover of hepatocytes and inflammation caused by cytokine release. This leads to the survival of poorly differentiated hepatocytes, which proliferate and develop into dysplastic nodules that can subsequently develop into HCC.[7]

Recently, diabetes has been demonstrated to be an independent risk factor for HCC. A meta-analysis showed that persons with diabetes had a 2.31-fold increased risk for development of HCC and a 2.43-fold increased risk of HCC mortality compared with nondiabetic persons.[8] In addition, a prospective study of 578,700 adults demonstrated that glucose levels were positively associated with the risk of HCC.[9] This mechanism of HCC development that is associated with diabetes may be driven by nonalcoholic steatohepatitis (NASH) and can occur even in noncirrhotic patients[10]; however, there is evidence in the literature that this may not be a strong association.[11,12]

Current Surveillance and Therapeutic Strategies

Due to the aggressive nature of HCC, surveillance is needed to decrease mortality from the disease; thus, it is important to identify high-risk patients and provide adequate surveillance. The objective of HCC surveillance is to detect new tumors at the earliest possible time point to increase the chance of survival, or if this is not possible, should, at minimum, provide a meaningful improvement in survival duration.[13] Surveillance is warranted in patients with HBV or HCV infection because their annual risk of HCC exceeds 0.2% and 1.5%, respectively.[13] In addition, patients with HBV or HCV infection who are coinfected with HIV are at a higher risk for rapidly progressive cirrhosis and subsequently the development of HCC.[14] Moreover, HCC in these patients is significantly more aggressive compared with HCC in patients infected with HBV or HCV alone.[15-17] As discussed previously, patients with cirrhosis of any etiology are ultimately at a higher risk for the development of HCC.[18] The current practice guidelines from the American Association for the Study of Liver Diseases, European Association for the Study of the Liver, and Asian Pacific Association for the Study of the Liver recommend noncontrast enhanced ultrasound screening every 6 months for patients in these high-risk groups.[13,19,20] Measurement of alpha-fetoprotein (AFP) levels is not recommended for surveillance or diagnosis due to poor sensitivity and specificity. In addition, the measurement of AFP is not cost-effective because it does not provide any additional value, unlike ultrasound surveillance.[21,22] With regard to effectiveness, a population-based study in the United States revealed that 6.6% of 3903 Medicare patients with HCC received regular surveillance prior to diagnosis.[23] This finding replicated the low rate of screening uptake (12%) among HCV-infected veterans with cirrhosis.[24] Thus, although the benefits of surveillance for HCC are known by most physicians and patients, surveillance for HCC is still not common practice.[25]

For patients diagnosed with HCC, initial management involves staging the tumor using the Barcelona Clinic Liver Cancer staging system.[26] HCC detected at early stages can be treated with curative procedures such as surgical resection, liver transplantation, and radiofrequency ablation. For intermediate and advanced cancers, treatment options include transarterial chemoembolization (TACE) alone or in combination with sorafenib (Nexavar, Bayer/Onyx), a kinase inhibitor. Patients who do not respond to TACE or who have more advanced HCC can be treated with sorafenib alone because its use has demonstrated a survival benefit.[27,28] This drug targets tyrosine protein kinases, such as vascular endothelial growth factor (VEGF) receptor and platelet-derived growth factor receptor as well as rapidly accelerated fibrosarcoma (RAF) kinases and c-Kit receptors.[29,30] Thus, this pharmacologic agent targets critical pathways involved in cell proliferation and survival.

Molecular Basis of Tumor Formation

The molecular pathogenesis of HCC is a complex process that involves the alterations of several regulators of the cell cycle. The most commonly involved genes are *TP53* (25%-40%) and *CTNNB1*/β-*catenin* (26%, associated with chronic HCV infection), although many other candidate driver mutations have been documented.[31] Important downstream effects of these mutations are seen on the signaling cascades of Ras and Rho (Figure 1) and epithelial

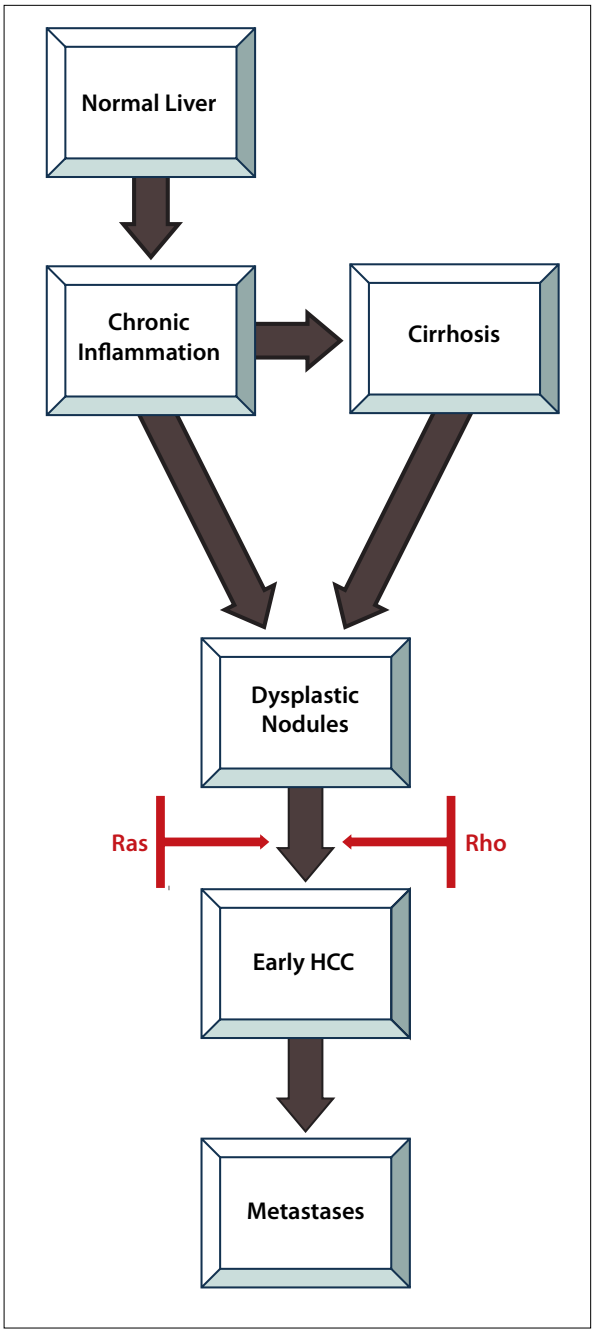

Figure 1. Mechanisms through which hepatocellular carcinoma (HCC) develops and the effect of Ras and Rho signaling pathways.

growth factor receptor, which are activated in over 50% of cases.[32] The tumor suppressor pathway involving the mammalian target of rapamycin is also often disrupted (40%-50%) in HCC.[33]

In addition, pathways involving angiogenesis have been shown to be of particular importance in HCC tumorigenesis due to the increased vascularity found in these tumors, and significant research efforts are ongoing to discover novel treatments that would inhibit the implicated molecular pathways.[34] Another important player in hepatocarcinogenesis is the activation of the *Myc* transcription factor. Mitogenic signaling cascades, including those involving the Wnt, sonic hedgehog, and epidermal growth factor molecules, lead to activation of this protein. Subsequently, *Myc* activation causes several changes in cell growth regulation. By increasing the production of cyclins and downregulating p21, *Myc* activation causes an increase in uncontrolled cell growth. Activated *Myc* also can downregulate the antiapoptotic Bcl-2 protein, favoring cell survival and escape from programmed cell death. Moreover, cells with activated *Myc* have upregulated levels of ribosomal RNA and corresponding proteins that contribute to increased cell proliferation. Cumulatively, these molecular changes play an important role in the development, proliferation, and survival of cancer cells that are further illustrated by studies showing that *Myc* inactivation can induce HCC regression.[35-37]

Statins: Development, Use, and Adverse Events

In 1978, the first therapeutic statin molecule was isolated from *Aspergillus terrus* and was later marketed by Merck Research Laboratories as lovastatin.[38] Since then, numerous clinical trials have provided a vast wealth of data on the safety and efficacy of these drugs. Statins belong to a class of drugs that inhibit the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This inhibition causes a reduction in cholesterol production in hepatocytes due to decreased levels of mevalonate, an intermediate in the cholesterol synthesis pathway. There are robust data correlating increased cholesterol levels with the risk of cardiovascular disease and stroke; therefore, statins are useful in the prevention of these diseases and will be of increased importance as obesity rates increase.[39] Clinical studies have demonstrated that statins are most effective for treating cardiovascular disease by secondary prevention.

An adverse effect of statin use that is of particular importance in the field of hepatology is the elevation of liver enzymes and possible liver injury, which has been deemed to be rare and unpredictable. Many healthcare providers continue to avoid statins in patients with chronic liver disease.[40] However, recent studies have demonstrated the safety of statins in patients with chronic liver disease, with maintenance of the associated benefits of decreasing the risk of cardiovascular events.[41] In general, statin toxicity seems to occur in less than 3% of all patients taking statins, and if toxicity is present, it also appears to be dose-dependent; however, many cases of statin toxicity spontaneously resolve.[41] One of these studies included a prospective, randomized, double-blind, placebo-controlled trial that investigated the safety

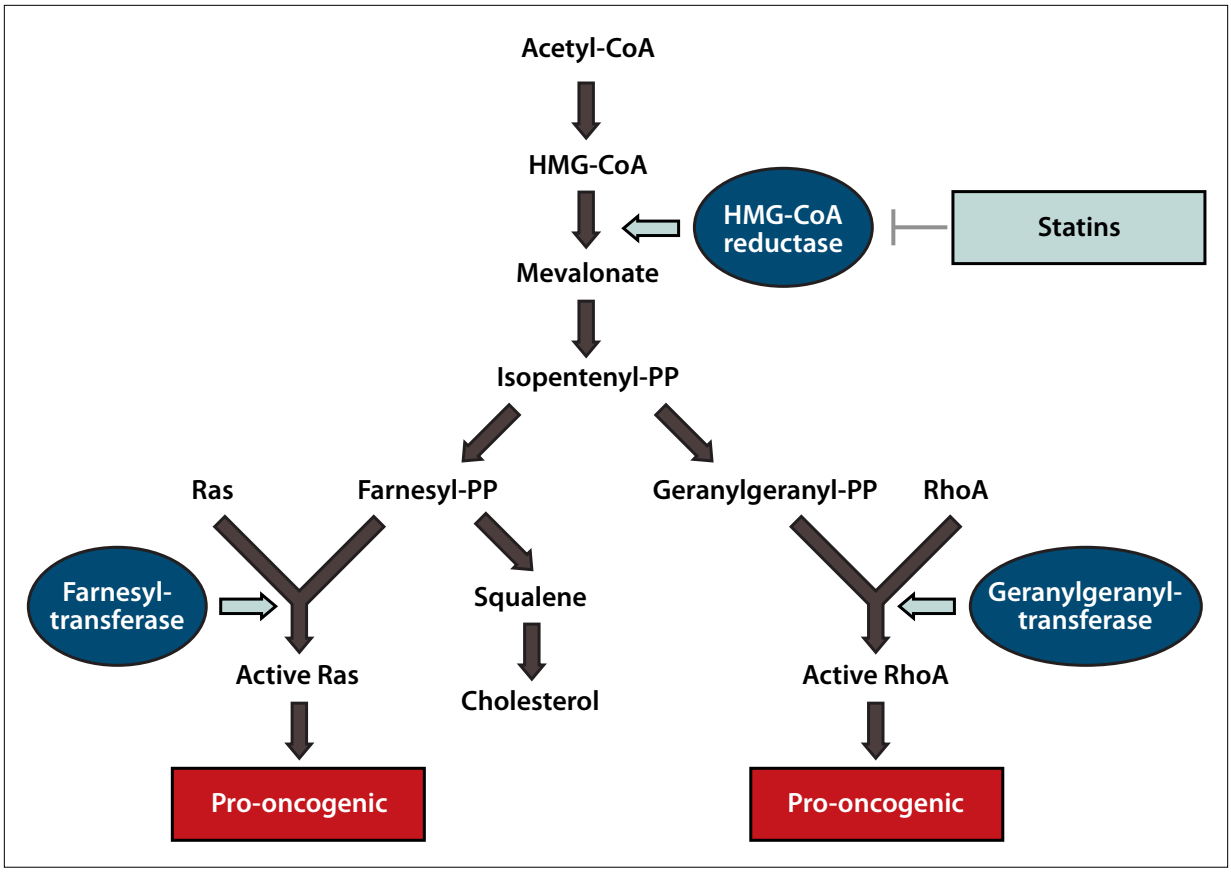

Figure 2. The mechanism of action of statins and the effect on Ras and Rho signaling pathways.
HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; PP, pyrophosphate.

of pravastatin in patients with NAFLD and chronic HCV infection. These patients were given pravastatin 80 mg/day for 36 weeks, and their lipid profiles and liver enzymes were measured. The results demonstrated a significant reduction in cholesterol, low-density lipoprotein (LDL), and triglycerides. Baseline alanine aminotransferase (ALT) levels doubled in only 7.5% of patients on pravastatin compared with 12.5% in the placebo group (P=.138). In addition, there was no difference seen in sustained ALT elevations between the 2 groups.[42]

In 2010, Athyros and colleagues conducted a post hoc analysis of the GREACE (Greek Atorvastatin and Coronary Heart Disease Evaluation) study.[43] The results of this analysis demonstrated a marked improvement in liver enzymes in patients treated with a statin compared with patients not treated with a statin. In addition, there was a 68% relative risk reduction of cardiovascular events among patients who were treated with a statin and had baseline ALT/aspartate aminotransferase elevations. Discontinuation of the statin due to adverse liver events was seen in less than 1% of those treated.[43] The safety of statins in patients with compensated chronic liver disease also has been shown in several cohort studies and randomized and retrospective analyses.[44-50]

Another possible effect of statins that had initially caused concern in the medical community was the contribution to increased cancer risk. However, studies looking at the risk of cancer in statin-treated patients have nullified this concern. In a retrospective cohort analysis conducted by Marelli and colleagues in 2011, 11 million adult Americans with no prior statin use demonstrated no statistically significant increase in risk of cancer with statin therapy.[51] A study by Friedman and colleagues involving over 360,000 patients with a follow-up of 9 years provided no evidence that statins cause cancer.[52] A meta-analysis of a large population of Japanese patients followed for over 70,000 patient-years found that there was no increase in cancer incidence or cancer-related death in patients treated with pravastatin.[53] However, statin therapy was reported to be associated with a 9% increased risk of development of diabetes in 91,140 patients included in this meta-analysis.[54]

Molecular Mechanism of Action of Statins

Statins competitively inhibit HMG-CoA reductase, which is the first enzyme of the HMG-CoA reductase pathway

that produces mevalonate, a building block of cholesterol (Figure 2). Because statins are similar to HMG-CoA on a molecular level, they take the place of HMG-CoA in the enzyme and reduce the rate by which it is able to produce mevalonate. By blocking this pathway, production of several other downstream molecules are also decreased, including geranylgeranyl pyrophosphate (GGPP). In addition to their lipid-lowering effects (which are known to be their main effect), statins have also been described to have other pleitrophic effects. Specifically, statins may also modulate inflammatory responses in the vasculature. Statins also increase LDL uptake via increased expression and synthesis of LDL receptors.[55] This increase in LDL receptor synthesis is believed to be accomplished via proteolytic enzymes that cleave sterol regulatory element-binding proteins, which then migrate to the nucleus and increase the expression of various products, including the LDL receptor. This increased synthesis of LDL receptor lowers the levels of circulating cholesterol by binding LDL molecules at the hepatocyte cell surface. Furthermore, statins have been shown to affect many pathways that regulate cell growth and survival through HMG-CoA reductase–dependent and –independent pathways. Interestingly, it has been also reported that statins suppress HCV replication in vitro.[56,57] This anti-HCV activity of statins has been thought to occur due to their antigeranylgeranylation effects of cellular proteins rather than their cholesterol-lowering activity.[58,59] However, statins may decrease the development of NASH through their effect on cholesterol metabolism.[60]

The Role of Statins in Preventing Cancer: Current Proposed Mechanisms

Although the definitive mechanisms by which statins decrease the incidence of HCC are not clear, there are several potential mechanisms involved. Statins have been well studied for the treatment of hypercholesterolemia; however, due to their mechanism of action, they affect cellular metabolism at multiple levels. One clinical outcome that has been of particular interest is the impact of statins on the development and progression of neoplasms. This effect has been well documented in vitro using cancers of multiple origins and treatment with different statins.[61] The response of neoplastic cells to different statins is highly individualized to the cell lineage. There also appears to be a lack of response in some cell lineages to the hydrophilic statins, such as pravastatin, in vitro.[62] The effect of statins on rapidly proliferating cells was also shown to be highly specific to genetically abnormal cells, with few effects seen on rapidly dividing normal human embryonic stem cells.[63]

The inhibition of growth in neoplastic cells in vitro by statins also has been investigated, and several mechanisms have been observed that are thought to mediate this process. These processes are thought to be affected directly by the inhibition of the production of mevalonate, an important precursor not only to cholesterol but also to ubiquinone and isoprenoids. The decreased production of isoprenoids prevents the posttranslational prenylation of small signaling G proteins important in cell survival and proliferation.[64]

The isoprenoid intermediates GGPP and farnesyl pyrophosphate (FPP) are of particular importance due to their interactions with the small GTP-binding Ras and Rho oncogenic proteins (Figure 2).[65] This family of proteins plays an integral role in cell survival and proliferation due to its pivotal role in multiple processes, including regulation of cell structure, support, motility, and replication.[66] This is thought to lead to an arrest in cell cycle progression through cellular changes in the production and processing of the mediators of cell division, the cyclins and cyclin-dependent kinases.[67]

Supporting evidence demonstrates that adding GGPP (or mevalonate, but not FPP or cholesterol) into the culture medium of human prostate cancer cells treated with lovastatin prevents arrest of the cell cycle and allows resumption of cellular division.[68] Furthermore, statins have been shown to cause apoptosis in cultured cancer cells through this same inhibition of the production of GGPP. Analysis of human thyroid cancer cells in vitro showed time-dependent dose responses to lovastatin with respect to the release of proapoptotic cytochrome c from the mitochondria; increases in caspase 2, 3, and 9 activity levels; and poly (adenosine diphosphate ribose) polymerase degradation, which was reversed following treatment with increasing levels of GGPP.[69] It has also been suggested that the effect on Rho and Ras may decrease resistance to chemotherapeutic agents (particularly doxorubicin) in cells that display multidrug resistance.

The impact of statins on angiogenesis is inconclusive; however, downstream effects of Rho on VEGF and endothelial cell migration suggest that statins should be antiangiogenic.[70,71] Conversely, statins are thought to upregulate endothelial nitric oxide synthase via promotion of protein kinase B, thus promoting angiogenesis.[71] Research suggests that the determinants of pro- vs antiangiogenic properties of a statin may lie in the concentration of the drug that can accumulate in exposed endothelial cells.[72] Statins also promote the growth inhibitory effects of p21 and p27 by inhibiting their breakdown via the proteasome pathway.[73] Additionally, statins can alter cell adhesion via HMG-CoA reductase–dependent and –independent pathways, causing anti-inflammatory and immunomodulatory effects in those treated with statins.[64] In addition, statins may prevent HCC through an indirect effect, namely by prevention of HCV replication, as described above, in infected persons.

Table. Studies Providing Evidence That Statins Can Reduce Hepatocellular Carcinoma (HCC) Risk

Year	Authors	Nation(s)	Study design	n=nonstatin user (n=HCC)	n=statin user (n=HCC)	Follow-up period (years)
2005	Friis S, et al[88]	Denmark	Cohort	12,251 (5)	336,011 (166)	3.3
2006	Sato S, et al[89]	Japan	Randomized controlled trial	179 (1)	84 (0)	5
2008	Friedman GD, et al[52]	United States	Cohort	NA	361,859 (42)	9.4
2009	El-Serag HB, et al[90]	United States	Case-control	NA	NA	2.4
2010	Matsushita Y, et al[53]	Japan	Meta-analysis	6349 (7)	7375 (5)	4.7-5.3
2011	Chiu HF, et al[91]	Taiwan	Case-control	NA	NA	4
2011	Marelli C, et al[51]	United States	Cohort	45,857 (19)	45,857 (5)	4.6-4.7
2012	Tsan YT, et al[85]	Taiwan	Cohort	30,626 (963)	2785 (58)	12
2012	Emberson JR, et al[92]	Europe, Australia, North America	Meta-analysis	87,087 (51)	87,062 (42)	4.8-5.1
2013	Tsan YT, et al[86]	Taiwan	Cohort	225,841(26,505)	35,023 (1378)	12

As previously mentioned, attention has been focused on mevalonate production and downstream molecules that are inhibited by statins. GGPP and FPP are 2 such end products that are crucial for the proliferation of malignant cells. Their absence leads to apoptosis via activation of the Ras and Rho pathways.[74-77] Statins also exert proapoptotic effects via a HMG-CoA reductase–dependent mechanism that activates caspases and decreases Bcl-2. This is mediated by regulating the RAF/mitogen-activated protein kinase 1 (MAPK)/extracellular signal-regulated kinase (ERK) pathway.[78,79] Statins also inhibit the proteasome pathway; thus, GGPP and FPP escape inactivation by degradation and can exert their cell growth inhibitory effects in cancer cells.[73,80] Additional mechanistic studies are needed to further investigate the mechanisms through which statins affect these pathways at the molecular level. Additional studies elucidating the possible mechanisms underlying the anti-HCC activity of statins may foster the use of statins in the treatment of HCC or enable the development of small molecules with more specific and potent anti-HCC activity.

Evidence for a Role of Statins in the Prevention of Hepatocellular Carcinoma: Laboratory and Epidemiologic Studies

In vivo, anticancer properties of statins were first suggested in 1996 when lovastatin induced a minor response lasting 8 months in a patient with anaplastic astrocytoma.[81] Since then, multiple studies have been conducted with statins for both prevention and treatment of cancers with varying results. In 2011, a study was published demonstrating that inhibition of HMG-CoA reductase, with atorvastatin in HCC cell lines, resulted in *Myc* phosphorylation and activation subsequently suppressing tumor growth and antiapoptotic pathways.[82] Another study showed that pitavastatin (Livalo, Kowa) can prevent liver tumorigenesis in obese mice, suggesting that statins may have a chemoprotective effect in obese persons.[83]

Amid the data showing the antitumorigenic effects of statins, interest has increased in recent years regarding the effects of statins on the risk of HCC, and several recent studies have shown that statins can have antineoplastic effects in HCC.[84] A cohort study of 33,413 HBV-infected persons in Thailand demonstrated a significant dose-response relationship for HCC prevention in patients receiving statins. The hazard ratios for patients after receiving 28 to 90 cumulative defined daily doses (cDDDs) compared with no statin was 0.66 (95% CI, 0.44-0.99), suggesting a significant preventative effect of statins on the development of HCC in patients infected with HBV.[85] Another cohort study of 260,864 patients with HCV infection, with a follow-up period of nearly 3 million person-years, demonstrated a reduced risk of HCC in HCV-infected patients taking statins. The adjusted hazard ratios were 0.66 (95% CI, 0.59-074) for those with 28 to 89 cDDDs, 0.47 (95% CI, 0.40-0.56) for those with 90 to 80 cDDDs per year, and 0.33 (95% CI, 0.25-0.42) for those treated with more than 180 cDDDs per year.[86] Furthermore, usage of statins as adjuvant therapy along with standard chemotherapeutic regimens seems promising in prolonging survival. A treatment regimen utilizing pravastatin was shown to increase median survival rates in patients with advanced HCC from 8 to 16 months (P=.006) when combined with the standard treatment of 5-fluorouracil and transcatheter arterial embolization compared with patients receiving

standard therapy alone.[87] The Table lists the various studies that have demonstrated a reduced risk of HCC in patients treated with statins.[51-53,85,86,88-92]

Singh and colleagues conducted a systematic review and meta-analysis to investigate the effects of statin use and the risk of HCC.[93] Seven observational studies and 3 studies reporting pooled data from 26 randomized controlled trials were included in the analyses. This comprehensive meta-analysis included data from more than 1.4 million patients with 4298 cases of HCC. The authors concluded that statin use was associated with a 37% reduction in the risk of HCC after adjusting for confounding variables. In this study, the effect on the incidence of HCC was greater among Asian populations compared with Western populations.[93] This can be explained by the fact that most cases of HCC in Asia and Sub-Saharan Africa are caused by viral hepatitis. In particular, HBV genome integration can lead to DNA microdeletions in the host DNA, causing changes in cell growth regulation via pathways such as MAPK.[94] In addition, the HBV X protein can upregulate various cell cycle control genes, such as *Ras, Raf, MAPK*, and *ERK,* leading to an increase in cell proliferation and survival.[95,96]

These changes may confer a growth advantage to neoplastic cells leading to the development of HCC in HBV-infected patients. As previously described, statins can inhibit these growth-promoting pathways and act as chemoprotective agents against liver tumorigenesis. In a similar manner, statins can inhibit the detrimental effects of HCV activation on the nuclear factor kB pathway, which causes inflammatory changes and immune activation leading to increased cell turnover, cirrhosis, and eventually malignant transformation.[97] Moreover, HCV can promote cell growth by downregulating growth arrest and DNA damage repair genes, such as *Gadd45*.[98] This can be countered by the antigrowth and apoptotic effects of statins.[64] In contrast, the mechanism by which statins reduce the risk of HCC in Western populations is less clear. A significant number of HCC cases in the Western world are associated with NAFLD and metabolic syndrome. Thus, the protective effect of statins in this population seems to involve modification of the metabolic syndrome, insulin-mediated cell proliferation, and reduction of obesity-associated inflammation.[93] Interestingly, a study by Tsan and colleagues in 2012 investigating the effects of statins on the risk of HCC in HBV-infected patients showed that risk reduction was independent of lipid-lowering effects, alluding to multiple mechanisms leading to antitumor activity.[85]

Shortcomings of the Currently Available Evidence and the Need for Future Studies

Although there is mounting evidence that statins have a chemoprotective effect on the prevention of HCC, several published studies examining this clinical outcome present conflicting results. In addition, it has been pointed out that selection or recall biases may play a role in the seemingly protective effect of statins in HCC prevention.[84] In contrast to observational studies, several randomized controlled trials of statins for the prevention of HCC have failed to demonstrate a protective effect. Specifically, in a post hoc examination of 22 randomized controlled trials involving statin therapy (Cholesterol Treatment Trialists' Collaboration), data from approximately 135,000 subjects yielded a total of 68 cases of HCC. It was concluded from this study that patients who were treated with statins were at equal risk for development of HCC compared with patients who were treated with placebo (adjusted odds ratio, 1.06; 95% CI, 0.66-1.71).[92] In addition, with regard to other cancers, the use of statins has been significantly associated with an increased risk of tumor progression in patients with bladder cancer. In 53% of the patients who took statins and were followed for this cancer, tumors became more aggressive; however, this finding was observed in only 18% of patients who did not take statins (P=.004; odds ratio, 4.9; 95% CI, 1.64-14.69).[99]

Unfortunately, most randomized controlled trials involving statins were carried out to study cardiovascular endpoints, and there are several limitations when these studies are used to examine cancer-related outcomes. Specifically, with regard to observational studies, it is difficult to determine the right dose, frequency, duration, and even when to initiate statins for cancer chemoprevention. Furthermore, due to the moderately low occurrence of HCC in the general population, designing these randomized controlled trials is logistically difficult. In addition, when factors such as patient dropout and mortality risks due to cirrhosis are considered, the volume of patients required to carry out such chemoprevention testing becomes much higher than predicted. Moreover, due to the clear correlation between viral hepatitis and the development of HCC, the need to delay antiviral therapy to reduce confounding factors would be ethically challenging. Finally, as mentioned previously, the chemopreventive effect of statins on HCC in comparison to the effects of anti-HCV therapy is still not clear.[100]

To account for these issues, a more robust analysis is needed because many of the aforementioned studies looked at cancer as a secondary outcome or were performed in patients with advanced disease. Although statins may be safe in cirrhotic patients,[101] this cohort requires increased attention for analysis of chemoprevention for HCC. Ultimately, large, properly planned cohort studies, with long and meticulous follow-up, on specific populations at increased risk for HCC would be more viable and better suited for the development of rigorous data to this end.

Conclusion

HCC is a major cause for cancer-related death worldwide, and early detection and treatment are extremely important for improving patient survival. Surveillance with semi-annual ultrasound screenings in high-risk patients is essential for early detection. However, decreasing the baseline risk of HCC development is paramount in improving survival of patients with chronic liver disease.

Statins have shown chemoprotective effects against several cancers, and their antiproliferative and apoptotic properties have been demonstrated in recent years. There is strong evidence that statin use in patients with chronic liver disease is safe and beneficial from a cardiovascular standpoint. Statin use in patients with chronic liver disease also has been associated with a reduced risk of development of HCC, although a precise mechanism that accounts for this reduction is lacking. In addition, adjuvant chemotherapy using a treatment regimen that includes a statin in patients with HCC is promising in prolonging survival.

Although a vast amount of data show the role of statins as chemoprotective agents, most of the studies have been observational and retrospective in nature. Therefore, there is a need for additional prospective cohorts and interventional studies to further support the role of statins in the prevention of liver tumorigenesis in humans as well as animal models. Moreover, continued research is warranted to elucidate the biochemical mechanisms of how statins affect the development of HCC. Future research should include substantiating the preventative role of statins in liver cancer so that the use of these drugs can be incorporated into current practice guidelines for the prevention and treatment of this aggressive cancer, especially in those with mild liver disease who may benefit the most from such therapeutic intervention.

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References

1. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients: the Cancer of the Liver Italian Program (CLIP) investigators. *Hepatology*. 1998;28(3):751-755.
2. Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. *J Clin Oncol*. 2009;27(9):1485-1491.
3. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin*. 2011;61(2):69-90.
4. Davila JA, Morgan RO, Shaib Y, McGlynn KA, El-Serag HB. Hepatitis C infection and the increasing incidence of hepatocellular carcinoma: a population-based study. *Gastroenterology*. 2004;127(5):1372-1380.
5. El-Serag HB. Epidemiology of hepatocellular carcinoma in USA. *Hepatol Res*. 2007;37(suppl 2):S88-S94.
6. Beasley RP. Hepatitis B virus. The major etiology of hepatocellular carcinoma. *Cancer*. 1988;61(10):1942-1956.
7. Budhu A, Wang XW. The role of cytokines in hepatocellular carcinoma. *J Leukoc Biol*. 2006;80(6):1197-1213.
8. Wang P, Kang D, Cao W, Wang Y, Liu Z. Diabetes mellitus and risk of hepatocellular carcinoma: a systematic review and meta-analysis. *Diabetes Metab Res Rev*. 2012;28(2):109-122.
9. Borena W, Strohmaier S, Lukanova A, et al. Metabolic risk factors and primary liver cancer in a prospective study of 578,700 adults. *Int J Cancer*. 2012;131(1):193-200.
10. Loria P, Lonardo A, Anania F. Liver and diabetes. A vicious circle. *Hepatol Res*. 2013;43(1):51-64.
11. Veldt BJ, Chen W, Heathcote EJ, et al. Increased risk of hepatocellular carcinoma among patients with hepatitis C cirrhosis and diabetes mellitus. *Hepatology*. 2008;47(6):1856-1862.
12. Yang WS, Va P, Bray F, et al. The role of pre-existing diabetes mellitus on hepatocellular carcinoma occurrence and prognosis: a meta-analysis of prospective cohort studies. *PLoS One*. 2011;6(12):e27326.
13. Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology*. 2011;53(3):1020-1022.
14. Pineda JA, Romero-Gómez M, Díaz-García F, et al; Grupo Andaluz para el Estudio de las Enfermedades Infecciosas; Grupo Andaluz para el Estudio del Hígado. HIV coinfection shortens the survival of patients with hepatitis C virus-related decompensated cirrhosis. *Hepatology*. 2005;41(4):779-789.
15. Puoti M, Bruno R, Soriano V, et al; HIV HCC Cooperative Italian-Spanish Group. Hepatocellular carcinoma in HIV-infected patients: epidemiological features, clinical presentation and outcome. *AIDS*. 2004;18(17):2285-2293.
16. Rosenthal E, Poirée M, Pradier C, et al; GERMIVIC Joint Study Group. Mortality due to hepatitis C-related liver disease in HIV-infected patients in France (Mortavic 2001 study). *AIDS*. 2003;17(12):1803-1809.
17. Bräu N, Fox RK, Xiao P, et al; North American Liver Cancer in HIV Study Group. Presentation and outcome of hepatocellular carcinoma in HIV-infected patients: a U.S.-Canadian multicenter study. *J Hepatol*. 2007;47(4):527-537.
18. Bruix J, Sherman M; Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. *Hepatology*. 2005;42(5):1208-1236.
19. Bruix J, Sherman M, Llovet JM, et al; EASL Panel of Experts on HCC; European Association for the Study of the Liver. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. *J Hepatol*. 2001;35(3):421-430.
20. Omata M, Lesmana LA, Tateishi R, et al. Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma. *Hepatol Int*. 2010;4(2):439-474.
21. Singal A, Volk ML, Waljee A, et al. Meta-analysis: surveillance with ultrasound for early-stage hepatocellular carcinoma in patients with cirrhosis. *Aliment Pharmacol Ther*. 2009;30(1):37-47.
22. Lok AS, Sterling RK, Everhart JE, et al; HALT-C Trial Group. Des-gamma-carboxy prothrombin and alpha-fetoprotein as biomarkers for the early detection of hepatocellular carcinoma. *Gastroenterology*. 2010;138(2):493-502.
23. Davila JA, Morgan RO, Richardson PA, Du XL, McGlynn KA, El-Serag HB. Use of surveillance for hepatocellular carcinoma among patients with cirrhosis in the United States. *Hepatology*. 2010;52(1):132-141.
24. Davila JA, Henderson L, Kramer JR, et al. Utilization of surveillance for hepatocellular carcinoma among hepatitis C virus-infected veterans in the United States. *Ann Intern Med*. 2011;154(2):85-93.
25. Sangiovanni A, Colombo M. Surveillance for hepatocellular carcinoma: a standard of care, not a clinical option. *Hepatology*. 2011;54(6):1898-1900.
26. Forner A, Reig ME, de Lope CR, Bruix J. Current strategy for staging and treatment: the BCLC update and future prospects. *Semin Liver Dis*. 2010;30(1):61-74.
27. Llovet JM, Ricci S, Mazzaferro V, et al; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008;359(4):378-390.
28. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol*. 2009;10(1):25-34.
29. Wilhelm SM, Adnane L, Newell P, Villanueva A, Llovet JM, Lynch M. Preclinical overview of sorafenib, a multikinase inhibitor that targets both Raf and VEGF and PDGF receptor tyrosine kinase signaling. *Mol Cancer Ther*. 2008;7(10):3129-3140.
30. Wilhelm S, Carter C, Lynch M, et al. Discovery and development of sorafenib: a multikinase inhibitor for treating cancer. *Nat Rev Drug Discov*. 2006;5(10):835-844.
31. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. *Lancet*. 2012;379(9822):1245-1255.
32. Villanueva A, Newell P, Chiang DY, Friedman SL, Llovet JM. Genomics and signaling pathways in hepatocellular carcinoma. *Semin Liver Dis*. 2007;27(1):55-76.
33. Villanueva A, Chiang DY, Newell P, et al. Pivotal role of mTOR signaling in hepatocellular carcinoma. *Gastroenterology*. 2008;135(6):1972-1983, 1983.e1-e11.
34. Fernández M, Semela D, Bruix J, Colle I, Pinzani M, Bosch J. Angiogenesis in liver disease. *J Hepatol*. 2009;50(3):604-620.

35. Denis N, Kitzis A, Kruh J, Dautry F, Corcos D. Stimulation of methotrexate resistance and dihydrofolate reductase gene amplification by c-myc. *Oncogene*. 1991;6(8):1453-1457.
36. Farazi PA, DePinho RA. Hepatocellular carcinoma pathogenesis: from genes to environment. *Nat Rev Cancer*. 2006;6(9):674-687.
37. Shachaf CM, Kopelman AM, Arvanitis C, et al. MYC inactivation uncovers pluripotent differentiation and tumour dormancy in hepatocellular cancer. *Nature*. 2004;431(7012):1112-1117.
38. Tobert JA. Lovastatin and beyond: the history of the HMG-CoA reductase inhibitors. *Nat Rev Drug Discov*. 2003;2(7):517-526.
39. Lewington S, Whitlock G, Clarke R, et al; Prospective Studies Collaboration. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. *Lancet*. 2007;370(9602):1829-1839.
40. Lewis JH. Clinical perspective: statins and the liver—harmful or helpful? *Dig Dis Sci*. 2012;57(7):1754-1763.
41. Calderon RM, Cubeddu LX, Goldberg RB, Schiff ER. Statins in the treatment of dyslipidemia in the presence of elevated liver aminotransferase levels: a therapeutic dilemma. *Mayo Clin Proc*. 2010;85(4):349-356.
42. Lewis JH, Mortensen ME, Zweig S, Fusco MJ, Medoff JR, Belder R; Pravastatin in Chronic Liver Disease Study Investigators. Efficacy and safety of high-dose pravastatin in hypercholesterolemic patients with well-compensated chronic liver disease: results of a prospective, randomized, double-blind, placebo-controlled, multicenter trial. *Hepatology*. 2007;46(5):1453-1463.
43. Athyros VG, Tziomalos K, Gossios TD, et al; GREACE Study Collaborative Group. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post-hoc analysis. *Lancet*. 2010;376(9756):1916-1922.
44. Vuppalanchi R, Teal E, Chalasani N. Patients with elevated baseline liver enzymes do not have higher frequency of hepatotoxicity from lovastatin than those with normal baseline liver enzymes. *Am J Med Sci*. 2005;329(2):62-65.
45. Avins AL, Manos MM, Ackerson L, et al. Hepatic effects of lovastatin exposure in patients with liver disease: a retrospective cohort study. *Drug Saf*. 2008;31(4):325-334.
46. Khorashadi S, Hasson NK, Cheung RC. Incidence of statin hepatotoxicity in patients with hepatitis C. *Clin Gastroenterol Hepatol*. 2006;4(7):902-907, quiz 806.
47. Segarra-Newnham M, Parra D, Martin-Cooper EM. Effectiveness and hepatotoxicity of statins in men seropositive for hepatitis C virus. *Pharmacotherapy*. 2007;27(6):845-851.
48. Henderson LM, Patel S, Giordano TP, Green L, El-Serag HB. Statin therapy and serum transaminases among a cohort of HCV-infected veterans. *Dig Dis Sci*. 2010;55(1):190-195.
49. Madhoun MF, Bader T. Statins improve ALT values in chronic hepatitis C patients with abnormal values. *Dig Dis Sci*. 2010;55(3):870-871.
50. Harrison SA, Rossaro L, Hu KQ, et al. Serum cholesterol and statin use predict virological response to peginterferon and ribavirin therapy. *Hepatology*. 2010;52(3):864-874.
51. Marelli C, Gunnarsson C, Ross S, et al. Statins and risk of cancer: a retrospective cohort analysis of 45,857 matched pairs from an electronic medical records database of 11 million adult Americans. *J Am Coll Cardiol*. 2011;58(5):530-537.
52. Friedman GD, Flick ED, Udaltsova N, Chan J, Quesenberry CP Jr, Habel LA. Screening statins for possible carcinogenic risk: up to 9 years of follow-up of 361,859 recipients. *Pharmacoepidemiol Drug Saf*. 2008;17(1):27-36.
53. Matsushita Y, Sugihara M, Kaburagi J, et al. Pravastatin use and cancer risk: a meta-analysis of individual patient data from long-term prospective controlled trials in Japan. *Pharmacoepidemiol Drug Saf*. 2010;19(2):196-202.
54. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet*. 2010;375(9716):735-742.
55. Ma PT, Gil G, Südhof TC, Bilheimer DW, Goldstein JL, Brown MS. Mevinolin, an inhibitor of cholesterol synthesis, induces mRNA for low density lipoprotein receptor in livers of hamsters and rabbits. *Proc Natl Acad Sci U S A*. 1986;83(21):8370-8374.
56. Ikeda M, Abe K, Yamada M, Dansako H, Naka K, Kato N. Different anti-HCV profiles of statins and their potential for combination therapy with interferon. *Hepatology*. 2006;44(1):117-125.
57. Delang L, Paeshuyse J, Vliegen I, et al. Statins potentiate the in vitro anti-hepatitis C virus activity of selective hepatitis C virus inhibitors and delay or prevent resistance development. *Hepatology*. 2009;50(1):6-16.
58. Ye J, Wang C, Sumpter R Jr, Brown MS, Goldstein JL, Gale M Jr. Disruption of hepatitis C virus RNA replication through inhibition of host protein geranylgeranylation. *Proc Natl Acad Sci U S A*. 2003;100(26):15865-15870.
59. Kapadia SB, Chisari FV. Hepatitis C virus RNA replication is regulated by host geranylgeranylation and fatty acids. *Proc Natl Acad Sci U S A*. 2005;102(7):2561-2566.
60. Lonardo A, Loria P. If steatosis is the atherosclerosis of the liver, are statins the "aspirin" for steatosis? *Dig Liver Dis*. 2012;44(6):451-452.
61. Osmak M. Statins and cancer: current and future prospects. *Cancer Lett*. 2012;324(1):1-12.
62. Shellman YG, Ribble D, Miller L, et al. Lovastatin-induced apoptosis in human melanoma cell lines. *Melanoma Res*. 2005;15(2):83-89.
63. Gauthaman K, Richards M, Wong J, Bongso A. Comparative evaluation of the effects of statins on human stem and cancer cells in vitro. *Reprod Biomed Online*. 2007;15(5):566-581.
64. Demierre MF, Higgins PD, Gruber SB, Hawk E, Lippman SM. Statins and cancer prevention. *Nat Rev Cancer*. 2005;5(12):930-942.
65. Maltese WA. Posttranslational modification of proteins by isoprenoids in mammalian cells. *FASEB J*. 1990;4(15):3319-3328.
66. Jaffe AB, Hall A. Rho GTPases: biochemistry and biology. *Annu Rev Cell Dev Biol*. 2005;21(1):247-269.
67. Relja B, Meder F, Wilhelm K, Henrich D, Marzi I, Lehnert M. Simvastatin inhibits cell growth and induces apoptosis and G0/G1 cell cycle arrest in hepatic cancer cells. *Int J Mol Med*. 2010;26(5):735-741.
68. Lee J, Lee I, Park C, Kang WK. Lovastatin-induced RhoA modulation and its effect on senescence in prostate cancer cells. *Biochem Biophys Res Commun*. 2006;339(3):748-754.
69. Zhong WB, Wang CY, Chang TC, Lee WS. Lovastatin induces apoptosis of anaplastic thyroid cancer cells via inhibition of protein geranylgeranylation and de novo protein synthesis. *Endocrinology*. 2003;144(9):3852-3859.
70. van Nieuw Amerongen GP, Koolwijk P, Versteilen A, van Hinsbergh VW. Involvement of RhoA/Rho kinase signaling in VEGF-induced endothelial cell migration and angiogenesis in vitro. *Arterioscler Thromb Vasc Biol*. 2003;23(2):211-217.
71. Vincent L, Chen W, Hong L, et al. Inhibition of endothelial cell migration by cerivastatin, an HMG-CoA reductase inhibitor: contribution to its anti-angiogenic effect. *FEBS Lett*. 2001;495(3):159-166.
72. Frick M, Dulak J, Cisowski J, et al. Statins differentially regulate vascular endothelial growth factor synthesis in endothelial and vascular smooth muscle cells. *Atherosclerosis*. 2003;170(2):229-236.
73. Rao S, Porter DC, Chen X, Herliczek T, Lowe M, Keyomarsi K. Lovastatin-mediated G1 arrest is through inhibition of the proteasome, independent of hydroxymethyl glutaryl-CoA reductase. *Proc Natl Acad Sci U S A*. 1999;96(14):7797-7802.
74. Chan KK, Oza AM, Siu LL. The statins as anticancer agents. *Clin Cancer Res*. 2003;9(1):10-19.
75. Danesh FR, Sadeghi MM, Amro N, et al. 3-Hydroxy-3-methylglutaryl CoA reductase inhibitors prevent high glucose-induced proliferation of mesangial cells via modulation of Rho GTPase/p21 signaling pathway: implications for diabetic nephropathy. *Proc Natl Acad Sci U S A*. 2002;99(12):8301-8305.
76. Blanco-Colio LM, Villa A, Ortego M, et al. 3-Hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors, atorvastatin and simvastatin, induce apoptosis of vascular smooth muscle cells by downregulation of Bcl-2 expression and Rho A prenylation. *Atherosclerosis*. 2002;161(1):17-26.
77. Takemoto M, Liao JK. Pleiotropic effects of 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitors. *Arterioscler Thromb Vasc Biol*. 2001;21(11):1712-1719.
78. Marcelli M, Cunningham GR, Haidacher SJ, et al. Caspase-7 is activated during lovastatin-induced apoptosis of the prostate cancer cell line LNCaP. *Cancer Res*. 1998;58(1):76-83.
79. Wu J, Wong WW, Khosravi F, Minden MD, Penn LZ. Blocking the Raf/MEK/ERK pathway sensitizes acute myelogenous leukemia cells to lovastatin-induced apoptosis. *Cancer Res*. 2004;64(18):6461-6468.
80. Shibata MA, Kavanaugh C, Shibata E, et al. Comparative effects of lovastatin on mammary and prostate oncogenesis in transgenic mouse models. *Carcinogenesis*. 2003;24(3):453-459.
81. Thibault A, Samid D, Tompkins AC, et al. Phase I study of lovastatin, an inhibitor of the mevalonate pathway, in patients with cancer. *Clin Cancer Res*. 1996;2(3):483-491.
82. Cao Z, Fan-Minogue H, Bellovin DI, et al. MYC phosphorylation, activation, and tumorigenic potential in hepatocellular carcinoma are regulated by HMG-CoA reductase. *Cancer Res*. 2011;71(6):2286-2297.
83. Shimizu M, Yasuda Y, Sakai H, et al. Pitavastatin suppresses diethylnitrosamine-induced liver preneoplasms in male C57BL/KsJ-db/db obese mice. *BMC Cancer*. 2011;11(1):281.
84. Lonardo A, Loria P. Potential for statins in the chemoprevention and management of hepatocellular carcinoma. *J Gastroenterol Hepatol*. 2012;27(11):1654-1664.
85. Tsan YT, Lee CH, Wang JD, Chen PC. Statins and the risk of hepatocellular carcinoma in patients with hepatitis B virus infection. *J Clin Oncol*. 2012;30(6):623-630.

86. Tsan YT, Lee CH, Ho WC, Lin MH, Wang JD, Chen PC. Statins and the risk of hepatocellular carcinoma in patients with hepatitis C virus infection. *J Clin Oncol*. 2013;31(12):1514-1521.
87. Kawata S, Yamasaki E, Nagase T, et al. Effect of pravastatin on survival in patients with advanced hepatocellular carcinoma. A randomized controlled trial. *Br J Cancer*. 2001;84(7):886-891.
88. Friis S, Poulsen AH, Johnsen SP, et al. Cancer risk among statin users: a population-based cohort study. *Int J Cancer*. 2005;114(4):643-647.
89. Sato S, Ajiki W, Kobayashi T, Awata N; PCS Study Group. Pravastatin use and the five-year incidence of cancer in coronary heart disease patients: from the prevention of coronary sclerosis study. *J Epidemiol*. 2006;16(5):201-206.
90. El-Serag HB, Johnson ML, Hachem C, Morgana RO. Statins are associated with a reduced risk of hepatocellular carcinoma in a large cohort of patients with diabetes. *Gastroenterology*. 2009;136(5):1601-1608.
91. Chiu HF, Ho SC, Chen CC, Yang CY. Statin use and the risk of liver cancer: a population-based case-control study. *Am J Gastroenterol*. 2011;106(5):894-898.
92. Emberson JR, Kearney PM, Blackwell L, et al; Cholesterol Treatment Trialists' (CTT) Collaboration. Lack of effect of lowering LDL cholesterol on cancer: meta-analysis of individual data from 175,000 people in 27 randomised trials of statin therapy. *PLoS One*. 2012;7(1):e29849.
93. Singh S, Singh PP, Singh AG, Murad MH, Sanchez W. Statins are associated with a reduced risk of hepatocellular cancer: a systematic review and meta-analysis. *Gastroenterology*. 2013;144(2):323-332.
94. Murakami Y, Saigo K, Takashima H, et al. Large scaled analysis of hepatitis B virus (HBV) DNA integration in HBV related hepatocellular carcinomas. *Gut*. 2005;54(8):1162-1168.
95. Nijhara R, Jana SS, Goswami SK, et al. Sustained activation of mitogen-activated protein kinases and activator protein 1 by the hepatitis B virus X protein in mouse hepatocytes in vivo. *J Virol*. 2001;75(21):10348-10358.
96. Tarn C, Lee S, Hu Y, Ashendel C, Andrisani OM. Hepatitis B virus X protein differentially activates RAS-RAF-MAPK and JNK pathways in X-transforming versus non-transforming AML12 hepatocytes. *J Biol Chem*. 2001;276(37):34671-34680.
97. Li ZH, Tang QB, Wang J, et al. Hepatitis C virus core protein induces malignant transformation of biliary epithelial cells by activating nuclear factor-kappaB pathway. *J Gastroenterol Hepatol*. 2010;25(7):1315-1320.
98. Higgs MR, Lerat H, Pawlotsky JM. Downregulation of Gadd45beta expression by hepatitis C virus leads to defective cell cycle arrest. *Cancer Res*. 2010;70(12):4901-4911.
99. Hoffmann P, Roumeguère T, Schulman C, van Velthoven R. Use of statins and outcome of BCG treatment for bladder cancer. *N Engl J Med*. 2006;355(25):2705-2707.
100. Singh S, Singh PP. Statins for prevention of hepatocellular cancer: one step closer? *Hepatology*. 2014;59(2):724-726.
101. Onofrei MD, Butler KL, Fuke DC, Miller HB. Safety of statin therapy in patients with preexisting liver disease. *Pharmacotherapy*. 2008;28(4):522-529.