The Role of Statins in Cancer Therapy

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Learning Objectives
After completing this course, the reader will be able to:
1. Explain how statins, used in the treatment of hypercholesterolemia, may be applicable to cancer prevention.
2. Discuss how statins potentially interfere with biologic processes relevant to cancer etiology.
3. Outline the gaps in our understanding in this area of theoretical versus applied medicine.

Abstract
Administration of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, to ambulatory patients is associated with a lower incidence of long-term adverse cardiovascular events, including death, myocardial infarction, stroke, atrial fibrillation, and renal dysfunction. However, increasing clinical evidence suggests that statins, independent of their effects on serum cholesterol levels, may also play a potential role in the prevention and treatment of cancer. Specifically, statins have been shown to exert several beneficial antineoplastic properties, including decreased tumor growth, angiogenesis, and metastasis. The feasibility and efficacy of statins for the prevention and treatment of cancer is reviewed. The Oncologist 2006;11:306–315

Introduction
3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, are commonly-used drugs for the treatment of hypercholesterolemia[1, 2]. Statins decrease low-density lipoprotein (LDL) cholesterol levels by inhibiting HMG-CoA reductase. HMG-CoA reductase in turn catalyzes the conversion of HMG-CoA into mevalonate and is the rate-limiting step in hepatic cholesterol biosynthesis [3]. Clinically, statin treatment is associated with a reduction in atherosclerotic plaque formation and a stabilization of pre-existing “vulnerable” atherosclerotic plaques [4]. Moreover, statins have been shown to decrease the incidence of adverse cardiovascular outcomes, including death, myocardial infarction, stroke, atrial fibrillation, and renal dysfunction in ambulatory patient populations [2, 5–13]. Statin administration is also associated with a lower incidence of adverse cardiovascular outcomes after invasive procedures such as percutaneous transluminal coro
nary angioplasty [9] and cardiac [14, 15], vascular [16–18], and noncardiovascular [19] surgery. However, the beneficial effects of statin therapy are not limited to patients with hypercholesterolemia. Several randomized clinical trials have shown that, even in patients with normal total and LDL cholesterol levels, statin administration is associated with less cardiovascular morbidity and mortality [7, 8]. Statins thus exert pleiotropic effects independent of their effects on cholesterol [20].

Although the exact mechanisms by which statins reduce the likelihood of cardiovascular events have yet to be fully elucidated, the metabolite of HMG-CoA reductase, mevalonic acid, is a precursor of cholesterol and the isoprenoid intermediates farnesyl and geranylgeranyl pyrophosphate. These intermediates are essential for the post-translational modification of intracellular G-proteins, such as Rho, Rac, and Ras, that regulate endothelial, platelet, and leukocyte function [21–23]. Statins have also been shown to modulate vascular remodeling by inhibiting cellular matrix metalloproteinases and transcription factors, such as nuclear factor-κB [23]. In patients with acute coronary syndromes or idiopathic dilated cardiomyopathy, statin therapy has been shown to reduce untoward inflammatory activity, including changes in C-reactive protein (CRP), serum amyloid A, tumor necrosis factor alpha (TNF-α), interleukin-6, and brain natriuretic peptide levels [21, 24, 25]. Moreover, statins have been reported to decrease serum levels of the inflammatory marker CRP within 14 days of administration, suggesting an acute protective role for these drugs [26]. Statins have also been shown to reduce tissue injury in models of ischemia and reperfusion in several organs, including the heart, lung, brain, kidney, and gut [19, 27–30]. Further, statins have been shown to attenuate vasoconstriction by increasing endothelial nitric oxide (NO) activity, a benefit seen within 6 weeks of the start of treatment [31]. Statins thus exert pleiotropic effects, independent of cholesterol reduction, that have direct antiatherosclerotic, antithrombotic, and anti-inflammatory impacts [23, 32–34].

Increasing evidence suggests that statins might be useful for cancer prevention and/or treatment through their interactions with essential cellular functions, such as cell proliferation and differentiation [35, 36]. For example, both in vitro and in vivo studies have demonstrated that statins inhibit tumor growth and induce apoptosis in a variety of tumor cells, including melanoma [37], glioma [38], neuroblastoma [39], and leukemia cell lines [40]. Additionally, several clinical trials have also assessed the antitumor activity of statins [41–46]. The potential role of statins in both cancer prevention and treatment is reviewed.

**Antitumor Effects of Statins**

**Inhibition of Tumor Cell Growth**

Cholesterol is a major structural component of cell membranes, and the cholesterol biosynthetic pathway is closely related to cell-growth processes. Statins reduce not only serum cholesterol levels but also mevalonate synthesis by inhibiting HMG-CoA reductase. Mevalonate is a precursor of several major products regulating the cell cycle, including dolichol, geranylpyrophosphate (GPP) and farnesylpyrophosphate (FPP) [3]. Dolichol has a stimulatory effect on DNA synthesis and is linked to several tumor cell proteins [47]. GPP and FPP cause isoprenylation of the intracellular G-proteins Ras and Rho, which in turn regulate the signal transduction of several membrane receptors crucial for the transcription of genes involved in cell proliferation, differentiation, and apoptosis.

Ras and Rho gene mutations are found in a variety of pancreas (90%), colon (50%), lung (30%), thyroid (50%), and myeloid leukemia (30%) tumor types [36]. Statins inhibit dolichol, GPP and FPP production, and block tumor cell growth in vitro and in vivo [48]. For example, lovastatin has been shown to stabilize the cell cycle kinase inhibitors p21 and p27, and to arrest breast cancer cell lines in the G1 phase of the cell cycle [49]. Similarly, cerivastatin has been demonstrated to inhibit Ras- and Rho-mediated cell proliferation [50]. These observations have led several investigators to hypothesize that statins might inhibit the growth of a variety of tumor cell types, including prostate, gastric, and pancreatic carcinoma, as well as colon adenocarcinoma, neuroblastoma, glioblastoma, mesothelioma, melanoma, and acute myeloid leukemia cells [42, 51–56]. Interestingly, statins also modify normal endothelial, fibroblast, and smooth muscle cell growth [57, 58]. However, normal cells appear to be more resistant to the antiproliferative effects of statins relative to tumor cells, which are much more likely to proliferate [59, 60].

**Inhibition of Angiogenesis**

Angiogenesis plays an important role in primary tumor growth and metastasis [61]. Statins have been reported to both stimulate [62–64] and inhibit [65, 66] blood vessel formation depending upon the tumor cell type [67]. For example, high-dose cerivastatin decreased tumor vascularization by 51% in a murine Lewis lung cancer model [68]. Statins have been shown to decrease vascular endothelial growth factor production [69] and to inhibit capillary tube formation [66, 70]. In contrast, statins have also been shown to stimulate protein kinase B, which in turn activates endothelial nitric oxide synthase (eNOS) and increases proangiogenic activity [64]. This NO-mediated effect depends
on caveolin, a protein that downregulates eNOS activity [71]. Endothelial cells with low caveolin expression seem to be extremely sensitive for statin-induced angiogenesis. Finally, there is growing evidence that the effects of statins on angiogenesis are concentration dependent. Weis et al. showed that low concentrations (0.5 mg/kg per day) of cerivastatin and atorvastatin enhanced endothelial cell proliferation, whereas high concentrations (2.5 mg/kg per day) significantly inhibited angiogenesis [68].

**Induction of Apoptosis**

Several experimental cancer models have shown that statins exert proapoptotic properties in a variety of tumor cells. For example, lovastatin induces a profound apoptotic response in cells derived from juvenile monomyelocytic leukemia, pediatric solid malignancies (e.g., rhabdomyosarcoma and medulloblastoma), malignant mesothelioma, astrocytoma, and squamous cell carcinoma of the cervix, head, and neck [50, 59, 72, 73]. Further, this statin-mediated apoptotic effect is also seen in cell lines treated with cerivastatin [74, 75]. In fact, Wong et al. found that cerivastatin is 10 times more potent in inducing apoptosis in acute myeloblastic leukemia (AML) cell lines than other statins [75]. Additionally, tumor cells themselves differ significantly in their sensitivity to statin-induced cell death. AML cells [76] and neuroblastoma cells [77] seem to be particularly sensitive to statin-induced apoptosis, whereas acute lymphoblastic leukemia cells are relatively insensitive.

Proposed mechanisms for statin-mediated apoptosis include an upregulation of proapoptotic protein expression (e.g., Bax, Bim) [78], combined with decreased antiapoptotic protein expression (e.g., Bcl-2) [40]. For example, lovastatin increases Bim protein levels and induces cell death in human glioblastoma cell lines [79]. These effects have been seen in both solid tumor and hematologic malignancies. Statins have also been shown to activate caspase proteases involved in programmed cell death. Cafforio et al. showed that cerivastatin caused cell death in human myeloma tumor cells by activating caspase-3, caspase-8, and caspase-9 [80]. Similarly, lovastatin induces apoptosis in prostatic epithelium and leukemia cells through activation of caspase-3 and caspase-7, respectively [81, 82].

**Repression of Tumor Metastases**

Several lines of evidence suggest that statins impair the metastatic potential of tumor cells by inhibiting cell migration, attachment to the extracellular matrix, and invasion of the basement membrane. In addition to reducing endothelial leukocyte adhesion molecule (e.g., E-selectin) [83] and matrix metalloproteinase (MMP)-9 expression [84], statins have been shown to inhibit epithelial growth factor–induced tumor cell invasion [60]. Both in vitro and in vivo studies have shown that fluvastatin and lovastatin reduce liver tumor formation and growth of established liver metastases in pancreatic cancer cell lines [85]. Similarly, atorvastatin has been shown to decrease melanoma cell metastasis [86]. Statins have also been shown to suppress lung metastasis of renal and mammary carcinoma cells [87, 88], as well as liver metastasis of colon adenocarcinoma cells [85, 89]. However, not all studies have confirmed that statins reduce tumor metastases. For example, lovastatin failed to inhibit colon carcinoma and glioblastoma cell migration and invasion [89].

The various antitumor effects of statin therapy are summarized in Figure 1.

**Statins and Cancer Risk/Prevention**

Experimental data suggesting a potential carcinogenicity and mutagenicity of statins date back to the early 1990s (Table 1). In vitro experiments of epithelial and fibroblastic cell lines showed that lovastatin induced prometaphase retardation and chromosome lagging during cellular metaphase and anaphase [90]. This led some to speculate that statins might interfere with centromere development and function, causing a mitotic disorder. Supporting this notion were studies demonstrating that simvastatin administered at a dose approximately 250 times higher than the dose normally used to treat hypercholesterolemia caused thyroid hyper trophy and follicular cell adenomas in rat strains [91]. Similarly, lovastatin administration at high dosage levels (500 mg/kg per day) was associated with a higher incidence of hepatocellular and pulmonary cancers [92]. Although fluvastatin was not found to cause liver tumors in rats and mice, it was found to be associated with a higher risk for thyroid neoplasms and forestomach papillomas in rodents [93]. Interestingly, statin-associated carcinogenicity in most of these studies was limited to dosages much higher than that commonly used to treat hypercholesterolemia in humans.

In contrast, other in vitro and in vivo studies have suggested that statins might exert an anticarcinogenic effect (Table 1). For example, toxicity studies in rats, dogs, and monkeys with lovastatin at doses up to 180 mg/kg per day demonstrated no carcinogenic effects [92]. Further, pravastatin and simvastatin were shown to suppress the development of 1,2-dimethylhydrazine–induced colon cancer in mice [94]. Similarly, pravastatin has been shown to reduce the incidence and volume of N-nitrosomorpholine–induced hepatic neoplastic nodules and to reduce N-methyl-N-nitrosourea–induced colon carcinogenesis [95, 96].

Further confusing the issue is the fact that human data regarding the cancer risk with statin administration are also conflicting (Table 2). A cohort study of more than 12,488 men and women revealed an inverse association...
between cholesterol level and cancer incidence, including lung, colorectal, pancreatic, and bladder cancers, and leukemia [97]. In contrast, several cholesterol-lowering trials have reported a tendency toward a higher number of cancer deaths in participants treated with cholesterol-lowering agents. The incidence of breast cancer in a prospective trial was 5.5% among pravastatin treated patients versus 0.3% in the placebo group [8]. Additionally, a retrospective analysis of 2,463 women revealed a 1.5-fold higher risk for breast cancer among statin users [98]. In a prospective study, conducted in elderly subjects, pravastatin was associated with a higher incidence of newly diagnosed gastrointestinal can-

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Table 1. Carcinogenic effect of statins: summary of experimental studies

<table>
<thead>
<tr>
<th>Procarcinogenic and mutagenic effects of statins</th>
<th>Study</th>
<th>Statin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction of prometaphase retardation and chromosome lagging during metaphase and anaphase [90]</td>
<td>In vitro</td>
<td>Lovastatin (100 mg)</td>
</tr>
<tr>
<td>Thyroid hypertrophy and follicular cell adenomas [91]</td>
<td>Sprague-Dawley rats</td>
<td>Simvastatin (100 mg/kg per day)</td>
</tr>
<tr>
<td>Higher incidence of hepatocellular and pulmonary cancers [92]</td>
<td>Rodents</td>
<td>Lovastatin (500 mg/kg per day)</td>
</tr>
<tr>
<td>Higher incidence of thyroid neoplasms and forestomach papillomas [93]</td>
<td>Mice and rats</td>
<td>Fluvastatin: Mice, 0.3–350 mg/kg per day; rats, 0.03–24 mg/kg per day</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anticarcinogenic effects of statins</th>
<th>Study</th>
<th>Statin</th>
</tr>
</thead>
<tbody>
<tr>
<td>No anticancer effect [92]</td>
<td>Rodents</td>
<td>Lovastatin (&lt;180 mg/kg per day)</td>
</tr>
<tr>
<td>Suppression of 1,2-dimethylhydrazine–induced colon cancer [94]</td>
<td>Mice</td>
<td>Pravastatin, 0.001%–0.01% in water; simvastatin, 0.01%–0.002% in food</td>
</tr>
<tr>
<td>Lower incidence of hepatic neoplastic nodules and colon carcinogenesis [95]</td>
<td>Sprague-Dawley rats</td>
<td>Pravastatin (10–20 mg/kg every other day)</td>
</tr>
</tbody>
</table>
Statins in Cancer Therapy

...cancers, although the difference did not reach statistical significance [1]. Furthermore, no difference in overall cancer incidence between the statin and placebo groups occurred in that trial. However, another study showed double cancer death rates, mainly of gastrointestinal cancers, in men with low serum cholesterol levels [99].

Several large investigations have failed to show a higher incidence of breast or gastrointestinal cancers, in men with low serum cholesterol levels [99].

...of breast or gastrointestinal cancer. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, for the primary prevention of cardiovascular events, and the Long-term Intervention with Pravastatin in Ischemic Disease trial revealed a similar relative risk for overall cancer development in the pravastatin and placebo groups [100, 101]. The Heart Protection Study found an equal incidence of any cancer subtype in simvastatin- and placebo-treated patients [102]. Moreover, later epidemiologic studies suggest that statins may prevent certain malignancies, including melanoma, and breast, colon, and prostate cancer [103–106]. In that regard, the Air Force/Texas Coronary Atherosclerosis Prevention Study, a case-controlled study, observed a 47% lower risk for colorectal cancer among long-term statin users (OR, 0.50; 95% CI, 0.40–0.63) [103]. Multivariate analysis further revealed that long-term statin therapy was also protective against colon cancer in high-risk patients, including those with a family history of colorectal cancer, hypercholesterolemia, ischemic heart disease, and inflammatory bowel disease, with an evaluated number needed to treat of approximately 2,400 patients. Interestingly, Graaf et al. reported a return to baseline risk for cancer development after withdrawal of statins, underpinning the potential protective effect of statins [110]. Finally, a systematic review of 10 cohort studies, two international studies, and 28 randomized trials revealed that low or reduced serum cholesterol concentrations were not associated with higher cancer mortality [111].

**Table 2. Statin therapy and the risk for cancer: summary of human clinical trials**

<table>
<thead>
<tr>
<th>Study</th>
<th>Statin</th>
<th>Cancer risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sacks et al. [8]</td>
<td>Pravastatin</td>
<td>5.2% ↑ incidence of breast cancer</td>
</tr>
<tr>
<td>Coogan et al. [98]</td>
<td>All statins</td>
<td>1.5-fold ↑ incidence of breast cancer; 1.2-fold ↑ incidence of prostate cancer</td>
</tr>
<tr>
<td>Shepherd et al. [1]</td>
<td>Pravastatin</td>
<td>0.4% ↑ incidence of overall cancer</td>
</tr>
<tr>
<td>ALLHAT-LLT trial [100]</td>
<td>Pravastatin</td>
<td>No higher cancer risk</td>
</tr>
<tr>
<td>LIPID trial [101]</td>
<td>Pravastatin</td>
<td>No higher cancer risk</td>
</tr>
<tr>
<td>Pedersen et al. [107]</td>
<td>Simvastatin</td>
<td>No higher cancer risk</td>
</tr>
<tr>
<td>Strandberg et al. [108]</td>
<td>Simvastatin</td>
<td>No higher cancer risk</td>
</tr>
<tr>
<td>Heart Protection Study [102]</td>
<td>Simvastatin</td>
<td>No higher cancer risk</td>
</tr>
<tr>
<td>AFCAPS/TexCAPS [7]</td>
<td>Lovastatin</td>
<td>50% ↓ incidence of melanoma</td>
</tr>
<tr>
<td>Poynter et al. [103]</td>
<td>All statins</td>
<td>47% ↓ incidence of colorectal cancer</td>
</tr>
<tr>
<td>Cauley et al. [104]</td>
<td>All statins</td>
<td>72% ↓ incidence of breast cancer</td>
</tr>
<tr>
<td>Blais et al. [109]</td>
<td>All statins</td>
<td>70% ↓ incidence of uterine cancer</td>
</tr>
<tr>
<td>Shannon et al. [106]</td>
<td>All statins</td>
<td>56% ↓ incidence of prostate cancer</td>
</tr>
</tbody>
</table>

Abbreviations: AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; LIPID, Long-term Intervention with Pravastatin in Ischemic Disease.

**STATINS AND CANCER TREATMENT**

Increasing evidence suggests that statins might enhance the antitumor activity of various cytokines and chemotherapeutic agents. For example, the combined administration of lovastatin and TNF-α has been shown to inhibit the proliferation of murine melanoma and leukemia cell lines and to prolong the survival of tumor-bearing mice [112, 113]. Synergistic...
interactions have also been reported between statins and chemotherapeutic agents such as cisplatin, 5-fluorouracil (5-FU), and doxorubicin. For example, pretreatment with lovastatin significantly increases 5-FU- and cisplatin-induced apoptosis in colon carcinoma cell lines [78]. Further, the antitumor effects of cisplatin have been shown to be augmented when combined withLovastatin in a murine melanoma model [114]. Lovastatin has also been shown to enhance paclitaxel-induced apoptosis in human leukemia cell lines [115]. Particularly interesting are the interactions between lovastatin and doxorubicin. As with other chemotherapeutics, lovastatin enhanced the antitumor activity of doxorubicin in murine melanoma, colon carcinoma, and lung carcinoma [116–118]. However, in addition to increasing the antitumor effect, lovastatin treatment was also associated with a lower risk for doxorubicin-associated cardiotoxicity [116, 119].

Several human clinical trials have investigated the antitumor effects of statins (Table 3). In a controlled, randomized trial of 91 patients with unresectable hepatocellular carcinoma, patients were randomly assigned to receive either pravastatin (20 mg/day for 2 weeks followed by 40 mg/day) or placebo concomitant with 5-FU chemotherapy [41]. None of the patients had to stop pravastatin as a result of toxicity. Further, the pravastatin-treated patients showed a reduction in tumor growth at 6 months and 1 year, and their median survival rate was double that of the control group. Similarly, a retrospective multivariate analysis of 349 patients with rectal cancer and neoadjuvant chemoradiation revealed that the response rate among statin users was fourfold higher than that of nonusers [120]. Finally, another case report described the inhibition of leukemic blast cell proliferation by lovastatin in AML patients [45].

Table 3. Statins for the treatment of cancer: summary of human clinical trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Statin</th>
<th>No. of patients</th>
<th>Type of cancer</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kawata et al. [41]</td>
<td>Pravastatin and 5-fluorouracil</td>
<td>91</td>
<td>Advanced hepatocellular carcinoma</td>
<td>Median survival rate: 18 months in the statin group vs. 9 months in the control group ($p &lt; .006$)</td>
</tr>
<tr>
<td>Lersch et al. [121]</td>
<td>Pravastatin</td>
<td>58</td>
<td>Hepatocellular carcinoma</td>
<td>Median survival rate: 7.2 months in the statin group vs. 5 months in the octreotide group and 3.5 months in the gemcitabine group</td>
</tr>
<tr>
<td>Katz et al. [120]</td>
<td>Statin and neoadjuvant chemoradiation</td>
<td>349</td>
<td>Resectable, nonmetastatic rectal cancer</td>
<td>Complete response rate: 30% in the statin group vs. 17% in the control group ($p = .01$)</td>
</tr>
<tr>
<td>Minden et al. [45]</td>
<td>Lovastatin</td>
<td>(Case report)</td>
<td>Acute myeloblastic leukemia</td>
<td>Statin therapy leads to an apparent control of the leukemic blast cells</td>
</tr>
<tr>
<td>Lopez-Aguilar et al. [122]</td>
<td>Fluvastatin</td>
<td>12</td>
<td>Pediatric tumors</td>
<td>22 months’ survival of two patients with anaplastic astrocytoma</td>
</tr>
<tr>
<td>Knox et al. [43]</td>
<td>Lovastatin</td>
<td>26</td>
<td>Squamous cell carcinoma of the head and neck</td>
<td>Stable disease in 23% of the patients</td>
</tr>
<tr>
<td>Vitols et al. [123]</td>
<td>Simvastatin</td>
<td>13</td>
<td>Chronic lymphocytic leukemia</td>
<td>No significant change in clinical disease status</td>
</tr>
</tbody>
</table>

However, not all clinical studies have yielded promising results. Pravastatin therapy as a treatment option for advanced hepatocellular carcinoma was not associated with a significantly better overall survival rate, although statin therapy seemed to be more beneficial than other new treatment options, including octreotide and gemcitabine therapy [121]. In a study using fluvastatin (8 mg/kg per day for 14 days every 4 weeks) in pediatric cancer patients, 10 of 12 patients died within 1–18 months because of their advanced disease stage, and laboratory assays demonstrated no significant changes during treatment [122]. Knox et al. conducted a phase I trial of Lovastatin administration (7.5 mg/kg per day for 21 consecutive days) in patients with recurrent or metastatic squamous cell carcinoma of the head and neck [43]. Although no objective improvements in tumor response were observed, 23% of the patients experienced stable disease for more than 3 months. Finally, in a study of 10 patients with chronic lymphocytic leukemia who received simvastatin (40 mg) daily for 2 weeks, no significant clinical change in the patients’ status was observed while taking the medication [123]. However, 40% of patients developed progressive disease during the subsequent year following statin withdrawal.

Several trials have examined the feasibility and safety of high-dose statins in cancer patients. In a phase I trial of lovastatin (2–45 mg/kg per day) in patients with solid tumors, no adverse side effects were seen with doses up to 25 mg/kg per day [46]. At doses above this level myopathy occurred, but coadministration of ubiquinone (coenzyme Q) significantly decreased the severity of myopathy. Another phase I/II study also showed that Lovastatin (20, 25, or 30 mg/kg for 7 days in cycles repeated monthly) was well tolerated...
in patients with malignant gliomas [44]. Only two patients experienced mild arthralgias, and even in the absence of ubiquinone, no myopathies were seen. Together, these data suggest that high-dose lovastatin is well tolerated and might have modest anticanic activity, especially in the treatment of brain tumors. In contrast, the antitumor activity of high-dose lovastatin has not been shown in patients with advanced gastric adenocarcinoma [42]. Sixteen patients received lovastatin (35 mg/kg per day for 7 consecutive days) with ubiquinone to prevent rhabdomyolysis. The treatment was repeated every 28 days. Two patients developed myalgia, and lovastatin administration had no antitumor effects in this patient population.

**CONCLUSION**

Statins are commonly prescribed drugs for the prevention of cardiovascular disease resulting from hypercholesterolemia. However, increasing evidence suggests that statins exert pleiotropic effects, independent of cholesterol reduction. In addition to their well-described antiatherosclerotic, antithrombotic, and anti-inflammatory properties, data obtained from both in vitro and in vivo studies suggest that statins also have antiproliferative, antiangiogenic, and antimetastatic properties. Statins may thus represent a novel therapeutic approach for cancer prevention and treatment.

Several important clinical questions remain to be addressed about the role of statins in cancer patients. First, the tumor types most susceptible to statin therapy have yet to be determined. Current preclinical and clinical data indicate that statins might be potentially useful for the treatment of melanoma [37], leukemia, brain cancer [38, 39], hepatocellular cancer [124], and squamous cell cancer of the head and neck [43, 59]. Second, it is not known which statins are most effective for cancer prevention and treatment. Although both hydrophilic (e.g., pravastatin and rusovastatin) and lipophilic (e.g., simvastatin and atorvastatin) statins demonstrate antitumor effects, hydrophilic statins are, in general, thought to be less effective intracellular agents. Nonetheless, hydrophilic statins, such as pravastatin, are associated with lower risks for colorectal [103] and hepatocellular cancer [41]. Third, the optimal statin regimen has yet to be defined. Statins alone are not effective anticanic agents. However, when combined with other cytotoxic agents, preclinical and clinical data suggest that statins may enhance chemotherapeutic effects. Most clinical trials to date have favored continuous, low-dose statin regimens over brief, high-dose statin regimens. This has been largely a result of the fact that low-dose regimens are associated with a lower risk for statin side effects, including myopathy, rhabdomyolysis, and hepatotoxicity. Moreover, statin side effects are more likely to occur in cancer patients, because they often receive concomitant medications, such as erythromycin and cyclosporine, which are known to interfere with statin metabolism through the hepatic cytochrome P-450 system [125].

In summary, statins may be beneficial for the prevention and treatment of cancer. Now is the time for appropriately designed clinical trials to underpin the promising data of pre-existing studies.

**DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST**

The authors indicate no potential conflicts of interest.


Hindler, Cleeland, Rivera et al.


100 Harmsen IC, Marschner IC, Hunt D et al. Relationship between lipid levels and clinical outcomes in the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Trial: to what extent is the reduction in coronary events with pravastatin explained by on-study lipid levels? Circulation 2002;105:1162–1169.


