Statins are potential anticancerous agents (Review)

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Abstract. Statins are inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), which is a rate-limiting enzyme in the mevalonate pathway. The pleiotropic effects of statins may be mediated by the inhibition of downstream products such as small GTP-binding proteins, Rho, Ras and Rac whose localization and function are dependent on isoprenylation. Preclinical studies of statins in different cancer cell lines and animal models showed antiproliferative, pro-apoptotic and anti-invasive effects. Notably, statins showed targeted action in cancerous cell lines compared to normal cells. Previous studies have also shown the synergistic effects of statins with chemotherapeutic agents and radiotherapy. This effect of statins was also observed in chemotherapeutic-resistant tumors. Statins were reported to sensitize the cells to radiation by arresting them in the late G1 phase of the cell cycle. Similarly, population-based studies also demonstrated a chemopreventive and survival benefit of statins in various types of cancers. However, this benefit has yet to be proven in clinical trials. The inter-individual variation in response to statins may be contributed to many genetic and non-genetic factors, including single-nucleotide polymorphisms in *HMGCR* gene and the overexpression of heterogeneous nuclear ribonucleoprotein A1, which was reported to reduce HMGCR enzyme activity. However, more studies with large phase III randomized controlled trials in cancer patients should be conducted to establish the effect of statins in cancer prevention and treatment.

Contents

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1. Introduction

The global burden due to cancer increased to 14.1 million new cases and 8.2 million cancer-associated mortalities in 2012 (1). The outcome of cancer patients remains poor, despite recent advances in the understanding of the molecular mechanism of tumorigenesis. Thus, more effective initial treatments for this intractable disease are required. Recent therapies under investigation include immunotherapy, chemotherapy, targeted molecular, antiangiogenic and gene therapy, radiation enhancement and drugs for overcoming resistance (2). Statins are inhibitors of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR), commonly used as cholesterol-lowering agents (3), that have proven their effectiveness in the treatment of cardiovascular diseases. Preclinical evidence has indicated their antiproliferative, pro-apoptotic, anti-invasive and radiosensitizing properties (4), and there are emerging interests in the use of statins as anticancer agents. In the present study, we reviewed the current data of statins in cancer.

2. Mechanism of action of statins

Inhibition of HMGCR by statins is a rate-limiting step in the mevalonate pathway. The products of the mevalonate pathway include isoprene units incorporated into sterol and non-sterol compounds. This inhibition by a statin may result in decreased levels of mevalonate and its downstream products, which affects critical cell functions such as membrane integrity, cell signaling, protein synthesis and cell cycle progression. The effect of statins on these processes and consequently on tumor cells, may therefore be able to control tumor initiation, growth and metastasis (Fig. 1) (5-17).

3. Antitumor effects of statins in preclinical studies

The *in vitro* preclinical studies in different cell lines have shown the ability of statins to suppress tumor growth and development. Statins exert antiproliferative, pro-apoptotic and anti-invasive effects in different cancer cell lines with varying sensitivity. The antimyeloma activity of statins in humans was first reported with the concomitant simvastatin administration in refractory multiple myeloma (MM), which showed reduced drug resistance (18). However, high-dose simvastatin treatment (15 mg/kg/day) in heavily pretreated MM patients transiently increased osteoclast activity and gastrointestinal side-effects, leading to premature discontinuation (19). A pre-operative study in primary invasive breast cancer patients

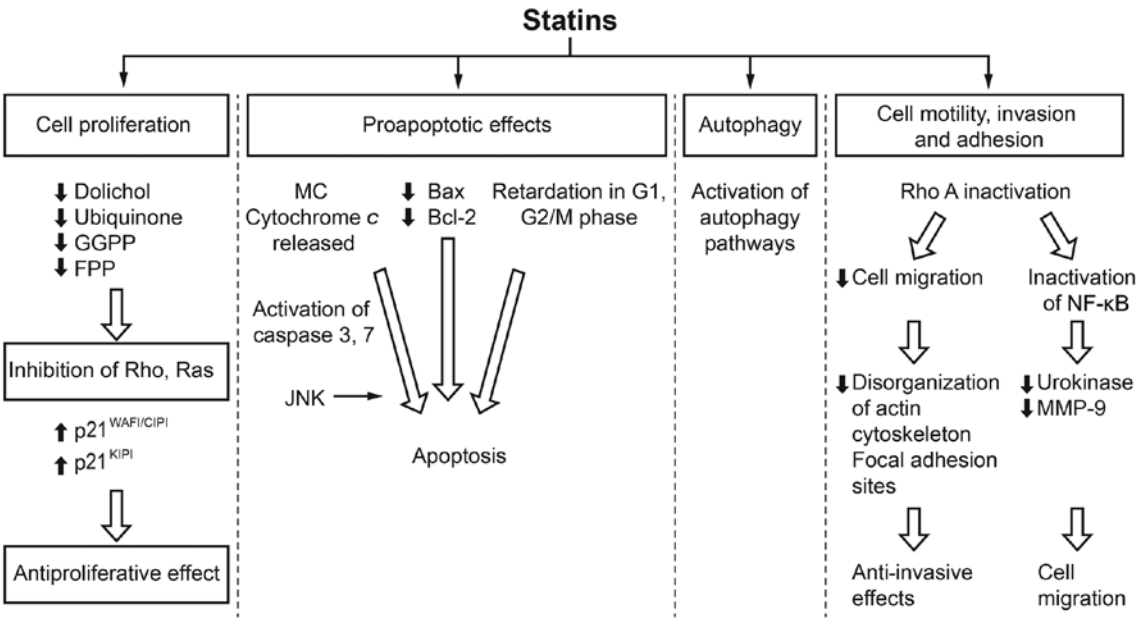

Figure 1. Pleiotropic effects of statins (5-17). Cyt, cytochrome *c*; FPP, farnesyl pyrophosphate; GGPP, geranylgeranyl pyrophosphate; $p21^{WAFI/CIP1}$ and $p27^{KIP1}$, two cyclin-dependent kinase inhibitors; JNK, c-jun NH2-terminal kinase; MC, mitochondria; MMP-9, matrix metalloproteinase-9; NF-κB, nuclear factor κB.

investigated atorvastatin-induced effects on tumor proliferation and HMGCR expression while analyzing HMGCR as a predictive marker for statin response. Results of that study suggest HMGCR is targeted by statins in breast cancer cells *in vivo*, and that statins may have an antiproliferative effect in HMGCR-positive tumors (20). Furthermore, fluvastatin reduced tumor proliferation and increased apoptotic activity in high-grade, stage 0/1 breast cancer in invasive breast cancer patients (21). Statin-induced effects and the underlined mechanism in different cancer cell lines are presented in Table I.

Besides their *in vitro* efficacy, statins have also been shown to have *in vivo* antitumor effects in various animal models of cancer. Their efficacy as chemopreventive agents has been demonstrated in radiation-induced mammary tumorigenesis (22), chemical-induced colon tumorigenesis in rodent models (23,24), human myeloid leukemia and glioma cancer cells inoculated in severe combined immunodeficient mice (25,26), and chemical-induced lung tumor in mice (27). Statins have also been shown to reduce metastasis in rat lymphoma (28), rat fibrosarcoma (29), mouse mammary tumor (30), murine colon tumor (31) and mouse melanoma (32). Furthermore, statins increased the *in vivo* antitumor effect of doxorubicin in three tumor models accompanied by attenuation of its cardiotoxicity (33). Similarly, statins increased the antitumor effect of tumor necrosis factor by inhibiting the tumor-induced angiogenesis in a murine tumor model (34). The effect of statin-induced anticancer activity in different animal models is presented in Table I.

4. Antitumor effects of statins in clinical studies

Observational and retrospective studies reporting cancer risk with statin usage. Accumulating evidence has focused on pre-diagnostic use of statins in reducing risk of lethal prostate cancer (35). In a prospective cohort study of 34,989 USA male health professionals, the use of statins was associated with a reduced risk of advanced prostate cancer. The risk of advanced disease was lower with longer statin use (P trend=0.003) vs. never use. The relative risk (RR) was 0.60 [95% confidence interval (CI), 0.35-1.03] for <5 years of use and 0.26 (95% CI, 0.08-0.83) for ≥5 years of use. There was no association between statin use and risk of total prostate cancer (RR, 0.96; 95% CI, 0.85-1.09) (36). In a Denmark-based case-control study (n=42,480), statin use was associated with an overall risk reduction (6%) that was specifically higher among patients with advanced prostate cancer (10%) (37). Similarly, a decreased risk in mortality was noted among 11,772 newly diagnosed non-metastatic prostate cancer patients in the UK. Furthermore, decreased risks of prostate cancer mortality and all-cause mortality were reported in patients who used statins prior to diagnosis [hazard ratio (HR), 0.55, 95% CI, 0.41-0.74; and HR, 0.66, 95% CI, 0.53-0.81, respectively]. The results were higher compared to those obtained from patients who initiated the treatment only after diagnosis (HR, 0.82, 95% CI, 0.71-0.96; and HR, 0.91, 95% CI, 0.82-1.01, respectively) (38). In another prospective, population-based cohort study (n=1001), statin use prior to prostate cancer diagnosis was unrelated to prostate cancer recurrence/progression, but was associated with a decrease in the risk of prostate cancer-specific mortality (39).

Data from observational studies have addressed the risk of glioma among statin users (40,41). The use of simvastatin and lovastatin for >6 months was inversely associated with glioma risk (40). A recent large nationwide case-control study (41) conducted in Denmark in patients with glioma (2,656 cases and 18,480 controls) also showed a reduction in the risk of glioma among long-term statin users compared with non-users, and the risk was inversely related to the intensity of statin treatment among users [odds ratio (OR), 0.71, 95% CI, 0.44-1.15 for highest intensity statin users]. This potential chemopreventive effect was limited to users of lipophilic statins (41).

Population-based studies have shown 19% reductions in esophageal cancer incidence where statins have been used.

Table I. Postulated molecular mechanisms of statin-induced anticancer activity in different cancer cell lines and animal models.

Authors, year (Refs.)	Statin	Cancer cell line/animal model used	Outcome	Molecular mechanism
Sławińska-Brych *et al*, 2014 (94)	Fluvastatin	C6 rat malignant glioma cells	Inhibitory and cytotoxic effect; no inhibition on the growth of normal neuronal cells	Decreased p-ERK1/2 expression, upregulation of p-JNK1/2, and reduction in the MMP-9 and VEGF concentrations
Yongjun *et al*, 2013 (95)	Atorvastatin	Microglia	Atorvastatin reduced the microglial expression of MT1-MMP	Downregulation of MT1-MMP is controlled by a p38 MAPK pathway in microglia
Crosbie *et al*, 2013 (96)	Statins	Human leukemic NK cell line	Statins inhibit YT-INDY proliferation, disrupt cell cycle progression and abrogate NK cell cytotoxicity	Blockage of products in the latter part of the mevalonate pathway
Al-Haidari *et al*, 2014 (97)	Simvastatin	CCL17-induced colon cancer cell (HT-29)	Dose-dependent decrease in cell migration	Inhibition of geranylgeranylation and RhoA activation
Ishikawa *et al*, 2014 (98)	Statins	Colorectal cancer cell lines	Simvastatin, fluvastatin and atorvastatin (except pravastatin) showed antiproliferative effects	Statins induced $p27^{KIP1}$ expression by downregulation of histone methyltransferase enhancer of EZH2
Chang *et al*, 2013 (99)	Simvastatin	HCT116 colorectal cancer cell	Apoptosis with a decrease in cell viability	Activation of p38MAPK-p53-survivin cascade; associated with the modulation of p21(cip/Waf1) and survivin
Rentala *et al*, 2013 (100)	Atorvastatin (16-64 μM)	CD133(+) CD44(+) cells derived from prostate cancer biopsies and peripheral blood	Dose-dependent inhibition of cell adhesion and cell differentiation	Decreased expression of integrins α1 and β1 and phosphorylated MYPT1 and FAK, reduced ROCK1 and FAK-mediated cell differentiation
Peng *et al*, 2013 (101)	Atorvastatin	LNCaP and PC3 human prostate cancer cells	Dose-dependent inhibition of proliferation; greater induction of autophagy in PC3 cells	Downregulation of Bcl2, upregulation of p21, and increased expression of LC3-II; upregulation of miR-182, which may be a stress-responsive mRNA
Al-Husein *et al*, 2013 (102)	Simvastatin	Human PC3 prostate cancer cells	Inhibition of transendothelial migration *in vitro*; direct activation of endothelial cells and enhancement of endothelial-barrier resistance	Inhibition of integrin αvβ3 activity and suppression of interaction between integrin αvβ3 and endothelial ICAM 1; modulation of angiopoietins and VEGF-A, thus preventing endothelial-barrier disruption
Fang *et al*, 2013 (103)	Simvastatin	Renal cell carcinoma cells, A498 and 786-O cells	Dose-dependent suppression of proliferation and motility; induction of apoptosis	Inhibition of AKT/mTOR, ERK, and JAK2/STAT3 pathways
Islam *et al*, 2013 (104)	Atorvastatin	*In vitro* and *in vivo* studies of HNSCC	Reduced cell motility, invasion, proliferation, and colony formation; inhibition of angiogenesis and lung metastases *in vivo*	Reduction in the active form of RhoC *in vitro*; a significant decrease in p-ERK1/2 and p-STAT3

Table I. Continued.

Authors, year (Refs.)	Statin	Cancer cell line/animal model used	Outcome	Molecular mechanism
Yu *et al*, 2013 (105)	Simvastatin	A549 Human lung cancer cell line	Blocks cells in G1 phase of the cell cycle and induces apoptosis	Decreased Bcl-2, increased Bax protein, downregulation of cyclin D1 and CDK expression, increased caspase-3, -8 and -9 mRNA and protein expression, downregulated XIAP levels, and decreased MMP-9 levels, possibly by inhibiting NF-κB
Pelaia *et al*, 2012 (106)	Simvastatin	Human non-small lung cancer cells	Induction of apoptosis after 36 h; increase in caspase-3 activation and TUNEL-positive cells, associated with a reduction in cell numbers	In susceptible lung cancer cell phenotypes, pro-apoptotic and anti-proliferative activity appears to be mediated by inhibition of the Ras/Raf/MEK/ERK signaling cascade
Chen *et al*, 2012 (107)	Atorvastatin	Human non-small cell lung carcinomas (NSCLCs)	Inhibits angiogenesis	Inhibition of VEGF expression *in vitro* and *in vivo* via inhibition of ROS production; ROS inhibited partly through suppression of Rac1/NADPH oxidase activity
Guterres *et al*, 2013 (108)	Simvastatin	Human metastatic melanoma cells (WM9)	Induction of a senescent phenotype, characterized by G1 arrest	Activation of p53/p21 pathway, and increased intracellular ROS accompanied by elevated expression of catalase and peroxiredoxin-1
Pich *et al*, 2013 (109)	Statins	Human metastatic melanoma cells	Melanoma cells more sensitive to *in vitro* lysis by NK cells	Increase of MICA involving peroxisome proliferator-activated receptor γ, which is independent of Ras and Rho signaling pathways
Gopalan *et al*, 2013 (110)	Simvastatin	Human breast cancer cells	Induces apoptosis	Activation of JNK/CHOP/DR5 pro-apoptotic pathway
Park *et al*, 2013 (111)	Simvastatin	TNBC cells	Decreased cell viabilities; PTEN mutant-type TNBC cells showed a decreased response vs. PTEN wild-type TNBC cells	Inhibition of TNBC cells via PI3K pathway activation
Zhao *et al*, 2012 (112)	Simvastatin	HER2-positive breast cancer cells	Time- and dose-dependent cell death in HER2-overexpressing cell lines	Inhibition of HER2 promoter and increased expression of PEA3 (HER2 promoter inhibitor)
Qi *et al*, 2013 (113)	Atorvastatin, fluvastatin and simvastatin	Lymphoma cells including A20 and EL4 cells	Statins induced apoptosis	Activation caspase-3, PARP and Bax; suppressed activation of anti-apoptotic molecule Bcl-2; increased intracellular ROS generation and p38 activation and suppressed activation of AKT and ERK pathways
Zeng *et al*, 2012 (114)	Simvastatin	SHI-1 Human acute monocytic leukemia cell line	Time- and dose-dependent inhibition of proliferation and induction of apoptosis	Change in gene expression level in PI3K-AKT signaling pathway
Yang *et al*, 2012 (115)	Atorvastatin	Human monocytic leukemia cells (THP-1)	Possible interaction with innate immunity	Significant decrease in the levels of TLR4 protein and mRNA, NF-κB expression and levels of TNF-α, IL-6 and IL-1β in LPS-induced THP-1 cells

Table I. Continued.

Authors, year (Refs.)	Statin	Cancer cell line/animal model used	Outcome	Molecular mechanism
Shi *et al*, 2013 (116)	Statins	Human esophageal squamous cell carcinoma (ESCC)	Inhibition of cell growth and proliferation	Decreased extracellular signal-regulated kinase activation and proliferating cell nuclear antigen, cyclin D1 expression, and increased cleavage of poly(ADP-ribose) polymerase
Ma *et al*, 2012 (117)	Lovastatin	Squamous cell carcinoma (SCC) cell lines SCC9 and SCC25	Synergistic cytotoxicity in combination with the EGFR inhibitor gefitinib	Targets multiple metabolic stress pathways including the LKB1/AMPK pathway
Tu *et al*, 2011 (118)	Simvastatin	Multiple myeloma cells	S-phase cell cycle arrest and apoptosis	Activation of Chk1, downregulation of Cdc25A, cyclin A and CDK2 expression; diminished Bcl-2 protein expression, increased cytosolic cytochrome *c* level, and activation of caspase 9 and 3
Araki *et al*, 2012 (119)	Hydrophobic statins	Rhabdomyosarcoma cells (A204 cells)	Autophagy	Depleting cellular levels of GGPP through an unknown pathway; induction of autophagy parallels statin toxicity (both can be suppressed by GGPP)
Animal model studies				
Jani *et al*, 1993 (32)	Lovastatin	Highly metastatic B16F10 mouse melanoma in nude mice	*In vitro* inhibition of attachment, motility and invasion that comprise the metastatic cascade	Antimetastatic effect on B16F10 cells is probably not mediated by a growth inhibitory action
Narisawa *et al*, 1996 (23)	Pravastatin	Colon tumor; 1,2-dimethylhydrazine.2HCl (DMH)-induced colon tumorigenesis was evaluated in ICR mice	Incidence of colon tumors at week 35 was significantly lower in the pravastatin-treated groups vs. the control group. However, pravastatin increased tumor multiplicity/tumor-bearing animal	Small dose of pravastatin may be related, at least in part, to modulation of cholesterol synthesis *in situ* at the colonic mucosa
Narisawa *et al*, 1996 (24)	Pravastatin	Colon tumor; N-methyl-N-nitrosourea-induced colon carcinogenesis in F344 rats	Incidence of colon carcinomas at week 40 was significantly lower in the 25 and 5 ppm groups vs. the control group. However, it was similar in the 200 ppm groups	Inhibition of the stage carcinogenesis (promotion), possibly through suppression of farnesyl isoprenylation of growth-regulating proteins such as p21 ras in the colonic mucosa
Broitman *et al*, 1996 (31)	D-limonene (non-toxic monoterpene)	CT-26, a murine transplantable colon tumor (hepatic 'metastasis' model)	Dietary mevalonate and d-limonene inhibited the growth of tumors both alone and in combination by ~80% vs. controls at day 35	D-limonene and mevalonate differentially affects the same pathway, and their individual actions may appear antagonistic *in vitro*
Hawk *et al*, 1996 (27)	Lovastatin	*In vitro* mouse and human non-transformed and neoplastically transformed lung epithelial cells; NNK-induced lung adenomas in mice	Inhibition of cell growth; no effect on tumor incidence or size, yet significant dose-dependent reduction in tumor multiplicity noted	Tumor suppression by lovastatin does not appear to be associated with the presence of mutated K-ras or to changes in K-ras expression

Table I. Continued.

Authors, year (Refs.)	Statin	Cancer cell line/animal model used	Outcome	Molecular mechanism
Liu *et al*, 2013 (120)	Simvastatin	Human lung cancer cell line A549 and Balb/c nude mouse were used	Significant inhibition of tumor cell invasion, growth and bone metastasis in lung cancer xenograft mouse model	Simvastatin may be associated with regulation of CD44, P53, MMP family and inactivation of MAPK/ERK signaling pathway
Inano *et al*, 1997 (22)	Simvastatin	Mammary tumor (Wistar-MS rats)	Increased development of ER^- PgR^- tumors and a reduced incidence of ER^+ PgR^+ tumors	Simvastatin has a potent preventive activity during the DES-dependent promotion/progression phase of radiation-induced mammary tumorigenesis
Alonso *et al*, 1998 (30)	Lovastatin	F3II sarcomatoid mammary carcinoma tumor model	*In vitro* inhibition of tumor cell attachment and migration; these actions were prevented by addition of mevalonate, but not by farnesyl pyrophosphate	These effects were not associated with the modification in Ras oncoproteins
Kikuchi *et al*, 1997 (26)	Simvastatin	Human glioma cell lines in nude mice	Inhibition of cell growth in all cell lines tested. Simvastatin showed additive effects on pLDL-induced cytotoxicity. Inhibition of cell growth after intra-tumoral injection of simvastatin and pLDL	Mevalonic acid or a metabolite in the cholesterol synthesis pathway is necessary for glioma cell growth
Clutterbuck *et al*, 1998 (25)	Simvastatin	SCID mice injected with human HL60 myeloblastic leukaemia cell line. HL60 bears an N-Ras mutation	Number of clonogenic HL60 cells was reduced in the bone marrow of mice that received simvastatin vs. control mice by 65 and 68%, respectively	Inhibition of AML cell proliferation by simvastatin may be independent of the Ras signaling pathway
Matar *et al*, 1998 (29)	Lovastatin	Rat fibrosarcoma	Short treatment with lovastatin diminished primary tumor growth and the number, and size of lung experimental metastasis	p21ras protein may have a significant role in metastatic behavior of tumor cells
Matar *et al*, 1999 (28)	Lovastatin	L-TACB rat lymphoma	No effect on cell motility, metalloprotease secretion, and neovascularization but significant inhibition of lymphoma cell invasiveness	Inhibition of invasiveness, possibly a consequence of impaired cell adhesion
Feleszko *et al*, 1999 (34)	Lovastatin	Ras-3T3 and HBL100-ras cells; Ha-ras-transformed murine tumor model	Inhibition of cells transformed with Ha-ras oncogene more effectively than control NIH-3T3 and HBL100 -neo cells in *in vitro* studies. In *in vivo* experiments, the Ras-3T3 tumor demonstrated significantly increased sensitivity to combined treatment with lovastatin and TNF-α vs. either agent alone	Lovastatin increases antitumor activity of TNF-α against tumor cells transformed with v-Ha-ras oncogene via inhibition of tumor-induced blood vessel formation (reduced VEGF production)
Feleszko *et al*, 2000 (33)	Lovastatin	Murine tumor cell lines (colon-26 cells, v-Ha-ras-transformed NIH-3T3 sarcoma cells, and Lewis lung carcinoma cells)	Significantly increased sensitivity to the combined treatment with lovastatin and doxorubicin vs. either agent alone	Lovastatin induced reduction of troponin T release by cardiomyocytes. Lovastatin is known to reduce doxorubicin-induced cardiac injury

Table I. Continued.

Authors, year (Refs.)	Statin	Cancer cell line/animal model used	Outcome	Molecular mechanism
Liao *et al*, 2013 (121)	Atorvastatin	LSL-KrasG12D-LSL-Trp53R172H-Pdx1-Cre mouse model (known as Pankras/p53 mice)	Significant increase in survival in mice fed 100 ppm atorvastatin vs. control mice with significant reduction in tumor volume and Ki-67-labeled cell proliferation	Atorvastatin inhibited prenylation in several key proteins, including Kras protein. Waf1p21, cyp51A1 and soluble epoxide hydrolase were crucial atorvastatin-targeted genes involved in inflammation and carcinogenesis
Vitols *et al*, 1997 (122)	*In vivo* study of malignant B lymphocytes from humans	Simvastatin orally, 40 mg daily for 12 weeks	Previously untreated B-cell chronic lymphocytic leukemia	Cells from four patients showed moderate to minor increases in the degradation rate of 1251-LDL, three patients showed an increase in HMGCR activity, and one patient showed both. No significant change in the clinical disease status was observed. However, during the subsequent year, 4/10 patients developed a therapy-demanding progressive disease
Higgins *et al*, 2012 (123)	Short-term biomarker modulation study	Simvastatin 40 mg orally daily for 24-28 weeks	The contralateral breast of women with a previous history of breast cancer was used as a high-risk model (n=50)	Total cholesterol, LDL cholesterol, triglyceride and hsCRP decreased significantly during the study (P-values: <0.001, <0.001, 0.003 and 0.05, respectively). Estrone sulfate concentrations decreased with simvastatin treatment (P=0.01 overall), particularly among post-menopausal participants (P=0.006)
Bjarnadottir *et al*, 2013 (20)	Window-of-opportunity trial	High-dose atorvastatin (i.e., 80 mg/day) was prescribed to patients for two weeks before surgery. Pre- and post-statin-paired tumor samples were analyzed for Ki67 and HMGCR immunohistochemical expression	Invasive breast cancer (n=50)	Upregulation of HMGCR was observed in 68% of the paired samples (P=0.0005). The average relative decrease in Ki67 expression was 7.6% (P=0.39) in all paired samples. The corresponding decrease in Ki67 expression in tumors expressing HMGCR in the pre-treatment sample was 24% (P=0.02). Furthermore, post-treatment Ki67 expression was inversely correlated to post-treatment HMGCR expression (rs, -0.42; P=0.03)

Table I. Continued.

ADP, adenosine diphosphate; AML, acute myeloid leukemia; AMPK, adenine monophosphate-activated protein kinase; CCL17, chemokine (C-C motif) ligand 17; CDK, cyclin-dependent kinase; CHOP, CCAAT/enhancer-binding protein homologous protein; DES, diethylstilbestrol; DR5, death receptor-5; ERK, extracellular signal-regulated kinase; ERK1/2, extracellular signal-regulated kinase 1 and 2; EZH2, enhancer of zeste homolog 2; FAK, focal adhesion kinase; GGPP, geranylgeranyl pyrophosphate; GI, gastrointestinal; HER2, human epidermal growth factor receptor 2; HMGCR, 3-hydroxy-3-methyl-glutaryl-CoA reductase; HNSCC, head and neck squamous cell carcinomas; hsCRP, high-sensitivity C-reactive protein; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; JAK, janus kinase; STAT3, signal transducer and activator of transcription 3; JNK 1/2, c-Jun N-terminal kinase 1 and 2; LC3-II, microtubule-associated protein 1A/1B-light chain 3-phosphatidylethanolamine conjugate; LDL, low-density lipid; LKB1, liver kinase B1; LPS, lipopolysaccharide; NNK, 4-(N-methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone; MAPK, mitogen-activated protein kinase; MICA, major histocompatibility complex (MHC) class I chain-related protein A; MMP-9, matrix metalloproteinase-9; MT1-MMP, membrane type 1 metalloproteinase; mTOR, mammalian target of rapamycin; MYPT1, myosin phosphatase target subunit 1; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor κB; NK, natural killer; PARP, poly(ADP-ribose) polymerase; pJNK, phosphorylated c-Jun N-terminal kinase; p-LDL, peroxidized low-density lipoprotein; $p21^{WAF1/CIP1}$ and $p27^{KIP1}$, two cyclin-dependent kinase inhibitors; p38MAPK, p38 mitogen-activated protein kinase; ppm, parts per million; PTEN, phosphatase and tensin homolog; ROCK1, Rho-associated kinase 1; ROS, reactive oxygen species; SCID, severe combined immunodeficient; TLR4, toll-like receptor 4; TNBC, triple negative breast cancer; TNF, tumor necrosis factor; TUNEL, terminal dUTP nick end-labeling; VEGF, vascular endothelial growth factor; VEGF-A, vascular endothelial growth factor A; XIAP, X-linked inhibitor of apoptosis protein.

Observational studies have shown that statins reduced the incidence of adenocarcinoma in patients with Barrett's esophagus (BE) by 43%; this effect was further enhanced by a 74% decrease in risk reduction in patients taking a combination of nonsteroidal anti-inflammatory drugs and statins (42).

Findings of a meta-analysis showed that statins are associated with a reduced risk of esophageal cancer, particularly in patients with BE. In a subset of patients with BE (5 studies, 312 esophageal adenocarcinomas in 2,125 patients), statins were associated with a significantly decreased risk (41%) of esophageal adenocarcinomas after adjusting for potential confounders (adjusted OR, 0.59, 95% CI, 0.45-0.78) (43). These findings were consistent with those of another meta-analysis of 11 observational studies. The pooled adjusted data showed statin use was associated with a lower incidence of the combined esophageal cancers (OR, 0.81, 95% CI, 0.75-0.88). Furthermore, their chemopreventive effect was increased in combination with cyclo-oxygenase inhibitors in reducing the risk of adenocarcinoma in BE (OR, 0.26, 95% CI, 0.1-0.68) (44).

A meta-analysis of 26 randomized controlled trials (RCTs) involving 290 gastric cancer and 8 observational studies, totaling 7,321 gastric cancers indicated a reduced risk of gastric cancer with statin use (45). In addition, a meta-analysis of published studies showed a modest reduction in colorectal cancer risk among statin users (46).

A review of 723 patients diagnosed with primary inflammatory breast cancer in 1995-2011 showed that hydrophilic statins were associated with significantly improved progression-free survival (PFS) rates (47). However, long-term use of statins was associated with increased risk of invasive ductal carcinoma (IDC; n=916) and invasive lobular carcinoma (ILC; n=1,068) in a contemporary population-based case-control study conducted in the Seattle-Puget Sound region. It was also reported that women diagnosed with hypercholesterolemia currently using statins for ≥10 years had more than double the risk of IDC (OR, 2.04, 95% CI, 1.17-3.57) and ILC (OR, 2.43, 95% CI, 1.40-4.21) compared with never users (48).

In the meta-analysis of all the observational studies published up to January 2012, statin use and long-term statin use did not significantly affect breast cancer risk. However, the cumulative meta-analysis showed a change in trend of reporting risk of breast cancer from positive to negative in statin users between 1993 and 2011. These findingd do not support the hypothesis that statins exert a protective effect against breast cancer (49).

The Cancer in The Ovary and Uterus Study (CITOUS; case-control study) assessed the use of statins prior to and following diagnosis in a subset of 424 cases of ovarian and endometrial cancers and 341 controls using pharmacy records. Use of statins >1 year prior to diagnosis was associated with risk reduction, whereas survival improvement was observed among the two malignancies when statins were ingested only after diagnosis (50).

The Nurses' Health and Health Professionals Follow-Up Study investigated the association between statin use and renal cell carcinoma (RCC) risk. The reported results were similar between ever vs. never users of statins. The subgroup analyses of that study reported that statin use may be associated with a lower risk of RCC among women with no history of hypertension (51).

Statin use is associated with a reduced risk of hepatocellular cancer, most strongly in Asian, but also in Western populations (52). Similarly, another meta-analysis suggested a favorable effect of statins on hepatocellular carcinoma in the absence of a duration-risk relationship (53).

A meta-analysis of all the published articles up to December 2007 showed no association between statin use on pancreatic cancer risk among patients using statins daily for managing hypercholesterolemia (54). These findings were consistent with those from another meta-analysis, which reported no association between statin use and pancreatic cancer risk among patients using statins daily for preventing cardiovascular event (55).

A meta-analysis of observational trials and RCTs did not support a protective effect of statins on overall lung cancer risk, and the lung cancer risk among elderly people (56). Nineteen studies (5 RCTs and 14 observational studies) involving 38,013 lung cancer cases suggested no association between statin use and risk of lung cancer (57). Similarly, a meta-analysis of published literature did not support the role of statins in prevention of skin cancer (58).

A retrospective evaluation of 1,502 patients with urothelial carcinoma of the bladder treated with radical cystectomy and pelvic lymphadenectomy without neoadjuvant therapy showed statin users were at a higher risk for disease recurrence and cancer-specific mortality in a univariate, but not a multivariate analysis. However, the present study also reported that statin users were older (P=0.003), had higher body mass index (median 32 vs. 28 kg/m^2, P<0.001), and were more likely to have positive soft tissue surgical margins (9 vs. 4%, P<0.001) (59). Another meta-analysis with limited RCTs suggested no association between statin use and risk of bladder cancer (60).

Numerous population-based case-control studies conducted in Taiwan did not provide evidence to support an association between statin use and risk of breast cancer (n=565; control, n=2,260) (61), esophageal cancer (n=197; controls, n=788) (62), bladder cancer (n=325; controls, n=1,300) (63), kidney cancer (n=177; controls, n=708) (64), and female lung cancer (n=297; controls, n=1,188) (65).

Another retrospective evaluation of the entire Danish population diagnosed with cancer between 1995 and 2007 was performed on 18,721 patients using statins regularly before the cancer diagnosis vs. 277,204 patients who had never used statins. The present study concluded that statin use in cancer patients was associated with reduced cancer-associated mortality as compared to that in non-users (HR, 0.85, 95% CI, 0.82-0.87) for each of the 13 types of cancer (66). In another meta-analysis (27 randomized trials), a median of 5 years of statin therapy was reported to have no effect on the incidence of, or mortality from, any type of cancer, or the aggregate of all cancers (67). The effect of statins on the incidence of different types of cancer reported in various observational and retrospective studies is presented in Table II.

Antitumor effect of statins in experimental studies

Lovastatin. In a phase I-II trial of lovastatin in anaplastic astrocytoma and glioblastoma multiforme, 18 patients received lovastatin between 20 and 30 mg/kg/day for 7 days followed by a 3-week rest. Lovastatin was considered well tolerated, as no patient reported myalgia and only 2 patients reported mild joint pain. Nine of 18 patients received concurrent radiation with no neurological toxicity, indicating that the combination was potentially safe. Of those who received concurrent radiation, 2 minor and 2 partial responses (duration range, 160-236 days) were observed. One patient each on lovastatin monotherapy showed partial and minor response, and stable disease. Notably, the patient who had partial response accomplished a response duration of >405 days, at which time lovastatin was discontinued due to cost-related issues (68).

Similarly, another phase I study evaluated the safety and tolerability of lovastatin using escalating doses in 88 cancer patients with advanced solid tumors. A majority of patients had prostate cancer or central nervous system tumors. Myopathy was found to be a dose-limiting toxicity and ubiquinone administration was associated with reversal of lovastatin-induced myopathy. Myopathy was prevented by its prophylactic administration in a 56-patient cohort. In the absence of supplementation, lovastatin was well tolerated up to 25 mg/kg/day for 7 days followed by a 3-week rest. One anaplastic astrocytoma patient treated with lovastatin at 30 and 35 mg/kg/day who progressed after surgical resection of the tumor, irradiation and 2 cycles of carmustine had a minor response (45% tumor size reduction) maintained for 8 months (69).

Prolongation of overall survival and PFS was documented in MM patients with lovastatin plus thalidomide and dexamethasone (TDL) vs. thalidomide and dexamethasone alone. The TDL regimen was safe and well tolerated (70).

Simvastatin. Simvastatin in combination with conventional FOLFIRI [irinotecan, 5-fluorouracil (5-FU), and leucovorin] in metastatic colorectal cancer patients showed promising antitumor activities (71). An exploratory subgroup analysis in non-small cell lung carcinoma patients with wild-type epidermal growth factor receptor (EGFR) non-adenocarcinomas showed higher RR, 40 vs. 0%, P=0.043) and longer PFS (3.6 vs. 1.7 months, P=0.027) with simvastatin plus gefitinib vs. gefitinib alone (72). Moreover, low-dose simvastatin to gemcitabine in advanced pancreatic cancer does not provide clinical benefit or results in increased toxicity (73).

Atorvastatin. The 6-month interventions with atorvastatin did not provide convincing evidence of colorectal cancer risk reduction in a multicenter phase II trial, although the relatively small sample size limited statistical power (74).

Fluvastatin. In patients with RCC and metastasis, zoledronate with fluvastatin or atorvastatin as bone-targeting therapy affected certain bone biomarkers and provided bone response in several patients. However, no statistically significant improvement in time to skeletal events was observed (75). The survival of pediatric brain stem tumor patients was significantly increased with metronomic treatment with carboplatin and vincristine associated with fluvastatin and thalidomide (76).

Pravastatin. In patients with acute myeloid leukemia (AML), pravastatin with idarubicin plus high-dose cytarabine (Ida-HDAC) decreased the total and low-density lipoprotein (LDL) cholesterol in almost all patients. The encouraging response rates suggest further trials evaluating the effect of cholesterol modulation on response in AML should be conducted (77). Chemoembolization and pravastatin combination significantly improved (P=0.003) survival of patients with advanced hepatocellular carcinoma vs. those receiving chemoembolization alone (78).

Table II. Effect of the use of statins on different types of cancer reported in various observational and retrospective studies.

Authors, year (Refs.)	Country and database used	Patient population	Tumor	Outcome
Platz *et al*, 2006 (36)	Prospective cohort study of USA male health professionals	Cancer-free participants (n=34,989) in 1990 followed to 2002. A total of 2,579 prostate cancer cases determined during 376,939 person-year, follow-up, of which 316 were advanced (regionally invasive, metastatic or fatal)	Prostrate cancer	Age-standardized incidence rates of advanced prostate cancer, 38 vs. 89 in current statin users vs. past or never users/100,000 person-years. Multivariable-adjusted relative risk for current statin use vs. no current use, advanced disease, 0.51 (95% CI, 0.30-0.86); metastatic or fatal disease, 0.39 (95% CI, 0.19-0.77)
Bansal *et al*, 2012 (124)	Literature search for observational studies through February 2012	Fifteen cohort and 12 case-control studies; included 56,847 prostate cancer cases (n=1,893,571) followed-up for 2-17 years	Prostate cancer	Significant reduction in the risk of total prostate cancer by 7% (RR, 0.93, 95% CI, 0.87-0.99, P=0.03) and clinically important advanced prostate cancer by 20% (RR, 0.80, 95% CI, 0.70-0.90, P<0.001)
Geybels *et al*, 2013 (39)	Patients (n=1,001) diagnosed with prostate cancer in 2002-2005 were followed-up by survey and the SEER registry (King Country, WA, USA)	Statin use was assessed by detailed in-person interview; 289 were ever users of statin drugs (n=1,001)	Prostate cancer	Prostate cancer recurrence/progression events, n=151; total deaths, n=123; prostate cancer-specific deaths, n=39. At 10 years, significantly lower risk of prostate cancer-specific mortality was reported for statin users (1%) vs. non-users (5%), P<0.01 (HR, 0.19, 95% CI, 0.06-0.56)
Park *et al*, 2013 (125)	Systematic search of literature through August 2012; 17 eligible studies from 794 references	This 13-study meta-analysis evaluated associations between statins and RFS following treatment of localized prostate cancer, among patients (n=21,185) treated primarily with RT vs. radical prostatectomy	Localized prostate cancer	Overall, statins did not affect RFS (HR, 0.90, 95% CI, 0.74-1.08). In RT patients (6 studies), statins were associated with a statistically significant improvement in RFS (HR, 0.68, 95% CI, 0.49-0.93) which was not observed in radical prostatectomy patients (7 studies)
Yu *et al*, 2014 (38)	Population-based electronic database, UK	Newly diagnosed patients (n=11,772; between 1998 and 2009) followed until 2012	Non-metastatic prostate cancer	Prostate cancer deaths (n=1,791); post-diagnostic statin use was associated with a decreased risk of prostate cancer mortality (HR, 0.76, 95% CI, 0.66-0.88) and all-cause mortality (HR, 0.86, 95% CI, 0.78-0.95)
Jespersen *et al*, 2014 (37)	Denmark-based case-control study, 1997-2010 from a national cancer registry	Patients (n=42,480) diagnosed with incident prostate cancer	Prostate cancer	Statin users had a 6% lower risk of prostate cancer vs. non-users (adjusted OR, 0.94, 95% CI, 0.91-0.97)
Ferris *et al*, 2012 (40)	Case-control study recruited newly diagnosed glioma cases and frequency-matched controls (Columbia University and the University of California San Francisco)	Recruited 517 glioma cases and 400 controls from 2007 to 2010	Glioma	Simvastatin and lovastatin showed significant inverse associations with glioma (OR, 0.49, 95% CI, 0.30-0.81 and OR, 0.47, 95% CI, 0.24-0.93, respectively). Statin intake for >120 months demonstrated the most significant associations (trend tests P=0.03)

Table II. Continued.

Authors, year (Refs.)	Country and database used	Patient population	Tumor	Outcome
Gaist *et al*, 2013 (41)	Nationwide case-control study in Denmark based on population-based medical registries	Patients with a first diagnosis glioma during 2000-2009 (n=2, 656 cases and 18,480 controls). Prior statin use, short-term (<5 years) and long-term (5^+ years)	Glioma	Glioma risk reduced among long-term statin users (OR, 0.76, 95% CI, 0.59-0.98) vs. never users, and was inversely related to the intensity of statin treatment among users (OR, 0.71, 95% CI, 0.44-1.15 for highest intensity)
Singh *et al*, 2013 (43)	Systematic search of databases through August 2012	Thirteen studies (one post-hoc analysis reporting 9,285 cases of of 22 RCTs) esophageal cancer among 1,132,969 patients	Esophageal cancer	Reported a significant reduction (28%) in esophageal cancer risk among patients on statins (adjusted OR, 0.72, 95% CI, 0.60-0.86)
Beales *et al*, 2013 (44)	Systematic search performed across multiple databases	Eleven observational studies. Studies examining adenocarcinoma development in BE: included 317 cancers and 1,999 controls. Esophageal cancers included 371,203 cancers and 6,083,150 controls	Esophageal cancer	In the Barrett's population, statin use (OR, 0.57, 95% CI, 0.43-0.75) was independently associated with a reduced incidence of adenocarcinoma
Wu *et al*, 2013 (45)	Literature search of databases up to March 2013	Three post-hoc analyses of 26 RCTs involving 290 gastric cancers and 8 observational studies, totaling 7,321 gastric cancers	Gastric cancer	Statins use significantly associated with a 27% reduction in gastric cancer risk (RR, 0.73, 95% CI,0.58-0.93), with considerable heterogeneity among studies [I (2): 88.9%]
Singh *et al*, 2013 (126)	Systematic search of multiple databases up to December 2012	Included 11 studies (8 observational and three post-hoc analyses of 26 clinical trials) reporting 5,581 cases of gastric cancer (n=5,459,975)	Gastric cancer	Statin use associated with significant reduction of 32% in gastric cancer risk (adjusted OR, 0.68, 95% CI, 0.51-0.91)
Lytras *et al*, 2014 (46)	Updated meta-analysis of published studies	Forty studies, involving >8 million subjects	Colorectal cancer	Risk of colorectal cancer with statin use was not statistically significant among RCTs (RR, 0.89, 95% CI, 0.74-1.07; n=8), but reached statistical significance among cohort studies (RR, 0.91, 95% CI, 0.83-1.00; n=13) and case-control studies (RR, 0.92, 95% CI, 0.87-0.98; n=19)
Undela *et al*, 2012 (49)	PubMed database and bibliographies of retrieved articles up to January 2012	Twenty-four (13 cohort and 11 case-control) studies including 76,759 breast cancer cases and >2.4 million participants	Breast cancer	Statin use and long-term statin use did not significantly affect breast cancer risk (RR, 0.99, 95% CI, 0.94-1.04 and RR, 1.03, 95% CI, 0.96-1.11, respectively)
McDougall *et al*, 2013 (48)	Population-based case-control study (Seattle-Puget Sound region)	Cases (916 IDC and 1,068 ILC) diagnosed between 2000 and 2008 were compared with 902 control women	Breast cancer	Current users of statins for ≥10 years had a 1.83-fold increased risk of IDC (95% CI, 1.14-2.93) and a 1.97-fold increased risk of ILC (95% CI, 1.25-3.12) vs. never users

Table II. Continued.

Authors, year (Refs.)	Country and database used	Patient population	Tumor	Outcome
Brewer *et al*, 2013 (47)	Retrospective cohort study (University of Texas, MD Anderson Cancer Center)	A total of 723 patients diagnosed with primary IBC in 1995-2011. Clinical outcomes were compared by statin use and type [weakly lipophilic to hydrophilic (H-statin) vs. lipophilic statins (L-statin)	Inflammatory breast cancer	H-statin use was associated with significantly improved PFS vs. no statin (HR, 0.49, 95% CI, 0.28-0.84; P<0.01); OS and DSS P-values were 0.80 and 0.85, respectively. For L-statins vs. no statin, P-values for PFS, DSS and OS were 0.81, 0.4 and 0.74, respectively
Lavie *et al*, 2013 (50)	Case-control study of newly diagnosed gynecological malignancies (CITOUS) (Clalit Health Services)	Statin use assessed in a subset of 424 cases of ovarian and endometrial cancers and 341 controls	Gynecological malignancies	Statin use >1 year prior to diagnosis associated with a significantly reduced risk of ovarian cancer (OR, 0.56, 95% CI, 0.33-0.94) and of endometrial cancer (OR, 0.59, 95% CI, 0.40-0.87)
Liu *et al*, 2012 (51)	Nurses' Health Study and Health Professionals Follow-Up Study	Statin use assessed in 80,782 women and 37,869 men, followed for 14 and 16 years, respectively	RCC	Two-hundred seventy seven incident RCC cases (164 women and 113 men) were identified. Multivariate RR of current statin use vs. no current use was 0.68 (95% CI, 0.46-1.00) in women and 1.17 (95% CI, 0.75-1.82) in men
Singh *et al*, 2013 (52)	Systematic search of databases through May 2012	Ten studies reporting 4,298 cases of hepatocellular carcinoma in 1,459,417 patients	Hepatocellular carcinoma	Although the results were heterogeneous [P=0.01, I (2): 59%], statin users were less likely to develop hepatocellular carcinoma vs. non-users (adjusted OR, 0.63, 95% CI, 0.52-0.76)
Pradelli *et al*, 2013 (53)	MEDLINE search until March 2012	Five observational studies based on 2,574 cases of hepatocellular carcinoma	Hepatocellular carcinoma	Statin treatment vs. no treatment was inversely related to hepatocellular carcinoma (summary RR, 0.58, 95% CI, 0.46-0.74). Between-study heterogeneity was significant (P<0.001) and numerically relevant (I, 65%)
Bonovas *et al*, 2008 (54)	Comprehensive search for relevant articles published up to December 2007	Twelve studies (3 randomized placebo-controlled trials, 4 cohort and 5 case-control studies)	Pancreatic cancer	No association between statin use and pancreatic cancer in randomized placebo-controlled trials (RR, 0.99, 95% CI, 0.44-2.21) or observational studies (RR, 0.86, 95% CI, 0.60-1.24)
Cui *et al*, 2012 (55)	Comprehensive search up to August 2011 for the relevant studies	Sixteen studies involving 1,692,863 participants and 7,807 pancreatic cancer cases	Pancreatic cancer	Non-significant decrease of pancreatic cancer risk among all statin users (RR, 0.89, 95% CI, 0.74-1.07). Significant heterogeneity detected among all studies (P<0.00001, I (2), 81%)

Table II. Continued.

Study name Authors, year (ref.)	Country and database used	Patient population	Tumor	Outcome
Deng *et al*, 2013 (56)	Meta-analysis of databases up to September 2013	Twenty-three studies (15 observational studies and 8 RCTs; n=4,864,582)	Lung cancer	No association between statins and lung cancer risk reported among RCTs (RR, 0.95, 95% CI, 0.85-1.06) or observational studies (RR, 0.89, 95% CI, 0.77-1.04). Similar association noted in elderly individuals (6 observational studies; RR, 1.03, 95% CI, 0.96-1.11)
Tan *et al*, 2013 (57)	Meta-analysis of the relevant articles in PubMed database up to March 2012	Nineteen studies [5 RCTs (n=29,658) and 14 observational studies (n=4,979,746)] involving 38,013 lung cancer cases	Lung cancer	No association reported for statin use and risk of lung cancer either among RCTs (RR, 0.91, 95% CI, 0.76-1.09), cohort studies (RR, 0.94, 95% CI, 0.82-1.07), or case-control studies (RR, 0.82, 95% CI, 0.57-1.16)
Li *et al*, 2014 (58)	Literature search of databases up to June 2013	Twenty-one articles with 29 studies	Skin cancer	No association between statin and skin cancer among melanoma (RR, 0.94, 95% CI, 0.85-1.04) and non-melanoma skin cancer (RR, 1.03, 95% CI, 0.90-1.19)
da Silva *et al*, 2013 (59)	Retrospective evaluation of records at 4 institutions	Patients treated with radical cystectomy and pelvic lymphadenectomy without neoadjuvant therapy (n=1,502)	Urothelial carcinoma of the bladder	Median follow-up, 34 months; statin use associated with disease recurrence (P≤0.05) and cancer-specific mortality (P≤0.02) on univariable Cox regression analysis
Zhang *et al*, 2013 (60)	Literature search of databases between January 1966 and October 2012	Thirteen studies (3 RCTs, 5 cohort and 5 case-control)	Bladder cancer	Non-significant increase in total bladder cancer risk among all statin users (RR, 1.07, 95% CI, 0.95-1.21). Long-term statin use did not significantly affect total bladder cancer risk (RR, 1.21, 95% CI, 0.92-1.59)
Nielsen *et al*, 2012 (66)	Entire Danish population	Between 1995 and 2007, among patients ≥40 years, 18,721 were regular statin users prior to cancer diagnosis and 277,204 never users	Cancer	Multivariate-adjusted HR for statin users vs. never users was 0.85 (95% CI, 0.83-0.87) for death from any cause and 0.85 (95% CI, 0.82-0.87) for death from cancer
Cholesterol Treatment Trialists' (CTT) Collaboration *et al*, 2012 (67)	Meta-analysis of individual patient records	Twenty-two randomized trials. of statin vs control (n=134,537) and 5 trials of more intensive vs. less intensive statin therapy (n=39,612)	Cancer	No effect of statins for~5 years on newly diagnosed cancer or death from such cancers [statin vs. control; cancer incidence, 3,755 (1.4%/year) vs. 3,738 (1.4%/year), RR, 1.00 (95% CI, 0.96-1.05); cancer mortality, 1,365 (0.5%/year) vs. 1,358 (0.5%/year), RR, 1.00 (95% CI, 0.93-1.08)]
Katz *et al*, 2005 (90)	Retrospective study	Any statin; median radiation therapy dose, 50.4 Gy (range, 45-55.8 Gy); evaluated in 349 and 308 patients (88%) receiving 5-FU-based chemotherapy	Non-metastatic rectal cancers	Thirty-three (9%) patients used a statin, with no differences in clinical stage vs. other 324 patients. At the time of surgery, metastatic disease was observed in 23 (7%) non-statin vs. 0 statin patients. Unadjusted pCR rates with and without statin use were 30 and 17%,respectively (P=0.10). ORs for statin use on pCR was 4.2 (95% CI,1.7-12.1; P=0.003) after adjusting for NSAID use, clinical stage and chemotherapy type

Table II. Continued.

Study name Authors, year (ref.)	Country and database used	Patient population	Tumor	Outcome
Graf H *et al*, 2008 (78)	Prospective cohort study	Fifty-two patients received TACE combined with pravastatin (20-40 mg/day) and 131 patients received chemoembolization alone; observation period of up to 5 years	Hepatocellular carcinoma	Thirty-one (23.7%) out of 131 patients treated with TACE alone and 19 (36.5%) out of 52 patients treated with TACE and pravastatin survived. Significant longer median survival of patients in the TACE and pravastatin group (20.9 months, 95% CI, 15.5-26.3, P=0.003) vs. TACE alone (12.0 months, 95% CI, 10.3-13.7)

BE, Barrett's esophagus; CI, confidence interval; CITOUS, The Cancer in The Ovary and Uterus Study; DSS, disease-specific survival; HR, hazard ratio; IBC, inflammatory breast cancer; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; NSAID, non-steroidal anti-inflammatory drug; OR, odds ratio; OS, overall survival; pCR, pathologic complete response; PFS, progression-free survival; RCC, renal cell carcinoma; RCT, randomized controlled trial; RFS, recurrence-free survival; RR, relative risk; RT, radiotherapy; TACE, transarterial chemoembolization.

Pravastatin in combination with epirubicin, cisplatin, and capecitabine did not improve outcome in advanced gastric cancer patients in a randomized phase II trial (79). Summary of clinical trials that used statins as monotherapy or as a combination in patients with different cancer types are presented in Table III.

5. Synergism of statins with radiotherapy and chemotherapy

Statins act by arresting cells in the late G1 phase of the cell cycle and can affect cell synchronization in the radiosensitive phase (5). The late G1 and G2-M phases are most sensitive to radiation therapy; therefore, statins potentially sensitized cells to radiation in the late G1 phase (80,81). The antitumor effect of lovastatin as a radiosensitizer on B-cell rat lymphoma (L-TACB) was higher than that of individual therapy (82). The underlying molecular mechanism involved Ras, which confers intrinsic resistance to radiation since *in vitro* studies using osteosarcoma cells demonstrated that lovastatin decreases this radiation resistance (80,81). Furthermore, HMGCR may serve as a predictive marker of response to postoperative radiotherapy in ductal carcinoma *in situ* (DCIS) (83). A retrospective cohort study suggested an association between statin therapy and improvement in response of rectal cancer to neoadjuvant chemoradiation (84).

Statins have shown anticancer potential with numerous chemotherapeutic agents. Simvastatin showed additive activity and mutual sensitization with doxorubicin by triggering caspase activation in human rhabdomyosarcoma cells (85). When combined with 5-FU or cisplatin as chemotherapy, lovastatin acts by inhibiting geranylgeranylation but not farnesylation of target protein(s) in colon cancer cells (10). Lovastatin or simvastatin with cytosine arabinoside significantly enhances the antiproliferative effect of each drug in leukemia cell lines and this may be beneficial in the leukemia treatment (86,87). A similar synergy of simvastatin with *N,N'*-bis(2-chloroethyl)-*N*-nitrosourea or β-interferon produces antiproliferative activity in human glioma cells (88). Cerivastatin also increases the cytotoxicity of 5-FU in chemoresistant colorectal cancer cell lines by inhibiting nuclear factor-κB DNA-binding activity (89).

A phase I study in AML patients showed synergistic effects of the addition of pravastatin to a conventional chemotherapy regimen (idarubicin and high-dose cytarabine) (77). Statin use in combination with concurrent chemoradiotherapy in preoperative rectal carcinoma patients was associated with improved pathologic complete response at the time of surgery (90). HMGCR expression was reported as an independent predictor of prolonged recurrence-free survival in primary ovarian cancer. Future studies are required to evaluate HMGCR expression as a surrogate marker of response to statin treatment, particularly in conjunction with current chemotherapeutic regimens (91). Synergistic effects are observed in patients with relapsed or refractory myeloma by the addition of lovastatin to thalidomide and dexamethasone (70).

6. Conclusion

Preclinical data based on cancer cell lines and animal models demonstrate encouraging anticancer activity of statins.

Table III. Summary of clinical trials that used statins as monotherapy or as combination in patients with different types of cancer.

Authors, year (Refs.)	Phase	Treatment regimen and duration	Patient population and tumor type	Treatment outcomes
Kornblau *et al*, 2007 (77)	I	Pravastatin (40-1,680 mg/day, days 1-8); Ida [(12 mg/(M2 x day), days 4-6] + high-dose cytarabine (Ara-C; HDAC) [1.5 g/(M2 x day) by CI, days 4-7]	AML; included 15 newly diagnosed, 22 salvage patients with unfavorable (n=26) or intermediate (n=10) prognosis cytogenetics	CR/CRp was obtained in 11 of 15 new patients including 8 of 10 with unfavorable cytogenetics and 9 of 22 salvage patients. An MTD for pravastatin + Ida-HDAC was not reached
Sondergaard *et al*, 2009 (19)	II	High-dose simvastatin (15 mg/kg/day) for 7 days followed by a 21-day rest in 24-week cycles	Heavily pretreated patients with multiple myeloma (n=6)	TRACP (osteoclast) activity in serum and levels of collagen fragments (NTX) in urine increased for all patients. No reduction in free monoclonal light chains or monoclonal proteins with high-dose simvastatin was observed. The study was terminated prematurely due to transient increase in osteoclast activity and gastrointestinal side-effects
Schmidmaier *et al*, 2007 (18)	II	Concomitant administration of simvastatin in myeloma patients refractory to two cycles of bortezomib or bendamustine during further two cycles	Refractory multiple myeloma (n=6)	Intrapatient (cycles I/II vs. III/IV) and interpatient comparison (vs. 10 patients without simvastatin) showed reduction of drug resistance
Hus *et al*, 2011 (70)	II	Thalidomide, dexamethasone and lovastatin (TDL group, 49 patients) or thalidomide and dexamethasone (TD group, 42 patients)	Relapsed or refractory myeloma	A 50% reduction of monoclonal band observed in 32% of TD and 44% of TDL patients, with prolongation of OS and PFS in the latter
van der Spek *et al*, 2007 (127)	II	Simvastatin 15 mg/kg/day was orally prescribed on days 1-7 of a 28-day cycle, divided into two daily dosages followed by rapid IV infusion of vincristine (0.4 mg) and doxorubicin (9 mg/m^2), and dexamethasone 40 mg (VAD) orally on day 7-10	Relapsed or refractory myeloma (n=12)	Treatment was feasible with mild side effects. However, only 1 of 12 patients achieved a PR
Larner *et al*, 1998 (68)	I-II trial	Lovastatin at doses between 20 and 30 mg/kg/day for 7 days followed by a 3-week rest, with or without radiation	Anaplastic astrocytoma and glioblastoma multiforme (n=18)	Monotherapy (N=9), one PR and one minor response; combined therapy (N=9), two minor and two PR; overall dose well tolerated without neurological toxicity
López-Aguilar *et al*, 2008 (76)	II	Patients received four courses of chemotherapy every 28 days [thalidomide alternating with fluvastatin every 14 days and combined with carboplatin and vincristine every 14 days followed by radiotherapy (56 cGy)] and four more courses of the same chemotherapy	Brain stem tumors (n=9)	Five patients had low-grade astrocytomas, three had glioblastoma multiforme, and one presented high-grade astrocytoma. Significant reduction in tumor volume and a significant increase in survival at 24 months observed

Table III. Continued.

Authors, year (Refs.)	Phase	Treatment regimen and duration	Patient population and tumor type	Treatment outcomes
Han *et al*, 2011 (72)	II	Gefitinib (G) alone or 250 mg/day, (n=54) or gefitinib plus simvastatin (GS) (250 and 40 mg/day, respectively, n=52). Each cycle of 4 weeks continued until disease progression or intolerable toxicity	Advanced non-small cell lung cancer	RR was 38.5% (95% CI, 25.3-51.7) for GS and 31.5% (95% CI, 19.1-43.9) for G. Median PFS was 3.3 (95% CI, 1.4-5.2) and 1.9 months (95% CI, 1.0-2.8) for GS and G, respectively. Median OS was 13.6 (95% CI, 7.1-20.1) and 12.0 months (95% CI, 7.8-16.2) for GS and G, respectively
Han *et al*, 2011 (128)	II	Irinotecan (65 mg/m^2) and cisplatin (30 mg/m^2) (n=61) on days 1 and 8 every 3 weeks until death or disease progression along with oral simvastatin (40 mg, daily)	Chemotherapy-naive patients with extensive-disease small cell lung cancer	One-year survival rate, 39.3%, median OS, 11 months; and median PFS, 6.1 months. Overall, RR, 75%
Konings *et al*, 2010 (79)	II	Six cycles of 3-weekly ECC with or without pravastatin (n=30) (40 mg once daily from day 1 of the first cycle until day 21 of the last cycle)	Advanced gastric carcinoma	ECC + pravastatin, PFR at 6 months, 6/14 patients (42.8%); RR, 5/15 (33.3%); median PFS and OS, 6 and 8 months, respectively ECC, PFR at 6 months, 7/15 patients; (46.7%); RR, 7/15 (46.7%) median PFS and OS, 5 and 6 months, respectively
Kim *et al*, 2001 (129)	II	Lovastatin 35 mg/kg/day for 7 consecutive days with ubiquinone (60 mg 4 times daily orally). Treatment was repeated every 28 days for 28 cycles. The median number of cycles was 2 (range, 1-4)	Advanced measurable gastric adenocarcinoma (n=16)	Fourteen patients were evaluated for response and toxicity. No patient achieved a response
Lee *et al*, 2009 (71)	II	Simvastatin oral 40 mg tablet once daily + conventional FOLFIRI chemotherapy. Treatment repeated every 2 weeks until disease progression or unacceptable toxicity	Metastatic adenocarcinoma of the colon or rectum (n=49)	ORR, ITT analysis, 46.9% (95% CI, 31.0-58.8), PP analysis, 45.8% (95% CI, 33.3-62.8); 1 complete response and 22 PRs. Disease-control rate, 83.7% (95% CI, 73.4-94.0). Median survival of all patients was 21.8 months (95% CI, 14.4-29.2); median TTP 9.9 months (95% CI, 6.4-13.3)
Limburg *et al*, 2011 (74)	II	(a) Atorvastatin 20 mg daily; (b) sulindac 150 mg twice daily; (c) oligofructose-enriched inulin (as ORAFTI® Synergy 1) 6 g twice daily; or (d) control (maltodextrin) 6 gm twice daily for 6 months	Previously resected colon cancer or multiple/advanced colorectal adenomas with ≥5 rectal ACFs at baseline (n=85)	76/85 Patients completed the trial. Median (SD) for % ΔACF was as below: atorvastatin, 5.6 (-69-143%) sulindac, -18.6 (-83-160%) ORAFTI® Synergy 1, -3.6 (-88-83%) control arms, -10.0 (-100-117%) No statistically significant comparisons of % ΔACF and within-arm or between-arm

Table III. Continued.

Authors, year (Refs.)	Phase	Treatment regimen and duration	Patient population and tumor type	Treatment outcomes
Manoukian *et al*, 2011 (75)	Pilot trial	Patients received zoledronate and fluvastatin or atorvastatin and followed for a median of 6 months	Renal cell carcinoma and bone metastasis (n=11)	Skeletal events, 7 (63%) patients; no skeletal events, 4 (36%) patients. Treatment response in 4 (36%) patients with the development of sclerosis in lytic bone lesions. Statistically significant differences in the median changes in biomarker levels between patients who had skeletal events and those who did not for DPD (P=0.03) and NTX (P=0.01), but not for BSAP (P=0.4)
Garwood *et al*, 2010 (21)	Peri-operative window trial	High-dose (80 mg/day) or low-dose (20 mg/day) fluvastatin for 3-6 weeks prior to surgery (n=45)	DCIS or stage 1 breast cancer	Twenty-nine paatients had paired Ki-67 primary endpoint data. Proliferation of high-grade tumors decreased by a median of 7.2% (P=0.008), which was statistically greater than the 0.3% decrease for low-grade tumors. More high-grade tumors had an increase in apoptosis (60 vs. 13%; P=0.015)
Lazzeroni *et al*, 2012 (130)	II	Participants were randomized to receive nimesulide 100 mg/day vs. simvastatin 20 mg/day vs. placebo for 1 year followed by a second year of follow-up	Women at higher risk for breast cancer (according to BRCAPRO), focused particularly on hormone non-responsive tumor risk (n=150)	Role of ductal lavage was evaluated to study endpoint biomarkers and the effects of these drugs on breast carcinogenesis. Preliminary results showed that the treatment is well tolerated and the safety blood tests do not show any significant liver toxicity
Hong *et al*, 2014 (73)	II	Three-week regimen with GS (gemcitabine 1,000 mg/m^2 on days 1, 8 and 15 plus simvastatin 40 mg once daily) or GP (gemcitabine 1,000 mg/m^2 on days 1, 8, and 15 plus placebo)	Advanced and metastatic pancreatic cancer (n=114)	Median TTP was 2.4 (95% CI, 0.7-4.1) and 3.6 months (95% CI, 3.1-4.1) in the GS and GP arms, respectively (P=0.903)
Thibault *et al*, 1996 (69)	I	Seven day courses of lovastatin given monthly at doses ranging from 2 to 45 mg/kg/day	Advanced solid tumors (most patients had prostate cancer or central nervous system tumor, n=88)	One minor response was documented in a patient with recurrent high-grade glioma
Kawata *et al*, 2001 (131)	II	Patients underwent TAE followed by oral 5-FU 200 mg (-1) day for 2 months and then randomized to control (n=42) and pravastatin (n=41) administered at a daily dose of 40 mg for 16.5±9.8 months (means ± SD)	Unresectable hepatocellular carcinoma (n=83)	Median survival was 18 months in pravastatin vs. 9 months in control (P=0.006)

Table III. Continued.

Authors, year (Refs.)	Phase	Treatment regimen and duration	Patient population and tumor type	Treatment outcomes
Lersch *et al*, 2004 (132)	II	Patients received 3x200 mcg/day octreotide for 2 months followed by 20 mg octreotide LAR every 4 weeks (n=30) or 40-80 mg pravastatin (n=20) or 80-90 mg/m^2 gemcitabine over 24 h weekly in cycles of 4 weeks (n=8)	Hepatocellular carcinoma (n=58)	Median OS was 5 months in octreotide, 7.2 and 3.5 months in the gemcitabine group. The difference between the pravastatin and gemcitabine groups was significant
Knox *et al*, 2005 (133)	I	Escalation of lovastatin starting at 5/mg/kg/day x 2 weeks, every 21 days, until MTD was reached; MTD was determined to be 7.5 mg/kg/day x 21days, every 28 days	Squamous cell carcinomas of the head and neck and of the cervix (n=26)	Median survival of patients, 7.5 months (mean 9.2±1.5 months). Stable disease for >3 months was observed in 23% of patients. One patient achieved stable disease and clinical benefit for 14 months in the study and a further 23 months off treatment. Disease stabilization rate of 23% was observed

ACF, aberrant crypt foci; AML, acute myeloid leukemia; BSAP, bone-specific alkaline phosphatase; CC3, cleaved caspase-3; CI, confidence interval; CR, complete remission; CRp, complete remission criteria met except that the platelet count was <100x10^9/l; DPD, deoxypyridinoline; ECC, epirubicin, cisplatin and capecitabine; FOLFIRI, irinotecan, 5-fluorouracil and leucovorin; Ida, idarubicin; ITT, intent-to-treat; MTD, maximum tolerable dose; NTX, N-telopeptide; ORR, overall response rate; OS, overall survival; PFR, progression-free rate; PFS, progression-free survival; PP, per protocol; PR, partial response; RR, relative risk; SD, standard deviation; TAE, transcatheter arterial embolization; TRACP, tartrate-resistant acid phosphatase; TTP, time to progression.

Similarly, several population-based and retrospective studies demonstrate chemopreventive and survival benefit of statins in various types of cancer. However, this benefit has not been confirmed/proven or validated in clinical trials, and is attributed to the absence of well-conducted large-scale phase III RCTs that have addressed the antitumor effects of statins in cancer. In fact, a majority of the trials thus far are phase I and/or small or poorly conducted phase II clinical trials with a small sample size and inadequate power. Moreover, genetic and non-genetic factors also may contribute to the inter-individual variation in statin response. In ovarian cancer, HMGCR expression was reported as an independent predictor of prolonged recurrence-free survival (91). Lipkin *et al*, identified a single-nucleotide polymorphism in the *HMGCR* gene that significantly modified the chemopreventive activity of statins for colorectal cancer risk (92). Heterogeneous nuclear ribonucleoprotein A1 (HNRNPA1) overexpression was recently reported to reduce HMGCR enzyme activity, enhance LDL-C uptake, and increase cellular apolipoprotein B (93). This may explain the inter-individual variation of drug response to statins. Advances in molecular biology may be useful to identify markers responsive to statin treatment and tailor base statin treatment based on genotypic profile, in the direction of personalized medicine.

Studies suggest statins can modulate the outcome of various cancer types and notably can target cancer vs. normal cells. The microenvironments seem to regulate the statin effect in different types of cancer. The side-effects appear to be limited, manageable and may be associated with genetic and non-genetic factors. Future studies should concentrate on evaluating statins in large-scale phase III RCTs in cancer patients to establish the precise effect of stains in cancer prevention and treatment.

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