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**ABOUT COVER**

Editorial board member of *World Journal of Clinical Oncology*, Dr. Takura is a Project Professor in the Department of Healthcare Economics and Health Policy, Graduate School of Medicine, University of Tokyo, Japan. He is part-time Research Fellow of the Cabinet Office and Chairman of the Specialized Agency of Cost-effectiveness Evaluation, Ministry of Health, Labour and Welfare. Dr. Takura also serves as a Guest Professor at Osaka University Graduate School of Medicine. Dr. Takura's research has focused on socioeconomic evaluation of cancer treatments and renal transplantation, and cost effectiveness analysis of revascularization for ischemic heart disease. His current approach to this work involves integrating big data from various sources. (L-Editor: Filipodia)

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## Statins in risk-reduction and treatment of cancer

Cristina I Barbalata, Lucia R Tefas, Marcela Achim, Ioan Tomuta, Alina S Porfire

**ORCID number:** Cristina I Barbalata 0000-0001-7265-7501; Lucia R Tefas 0000-0001-8943-8938; Marcela Achim 0000-0002-0184-3144; Ioan Tomuta 0000-0002-5094-008X; Alina S Porfire 0000-0001-8475-2792.

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**Cristina I Barbalata, Lucia R Tefas, Marcela Achim, Ioan Tomuta, Alina S Porfire,** Department of Pharmaceutical Technology and Biopharmaceutics, Faculty of Pharmacy, "Iuliu-Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca 400012, Romania

**Corresponding author:** Alina S Porfire, PhD, Associate Professor, Department of Pharmaceutical Technology and Biopharmaceutics, Faculty of Pharmacy, "Iuliu-Hatieganu" University of Medicine and Pharmacy, 41 Victor Babes, Cluj-Napoca 400012, Romania. [aporfire@umfcluj.ro](mailto:aporfire@umfcluj.ro)

### Abstract

Statins, which are competitive inhibitors of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase, reduce cholesterol blood levels and the risk of developing cardiovascular diseases and their related complications. In addition to this main activity, statins show pleiotropic effects such as antioxidant, anti-inflammatory and antiproliferative properties, with applications in many pathologies. Based on their antiproliferative properties, *in vitro* and *in vivo* studies have investigated their effects on various types of cancer (*i.e.*, breast cancer, prostate cancer, colorectal cancer, ovarian cancer, lung cancer) with different genetic and molecular characteristics. Many positive results were obtained, but they were highly dependent on the physiochemical properties of the statins, their dose and treatment period. Combined therapies of statins and cytotoxic drugs have also been tested, and synergistic or additive effects were observed. Moreover, observational studies performed on patients who used statins for different pathologies, revealed that statins reduced the risk of developing various cancers, and improved the outcomes for cancer patients. Currently, there are many ongoing clinical trials aimed at exploring the potential of statins to lower the mortality and the disease-recurrence risk. All these results are the foundation of new treatment directions in cancer therapy.

**Key words:** Statins; Cancer; Pleiotropic effects; Risk reduction; Clinical trials; 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; Mevalonate pathway

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**Core tip:** In the last few years, statins have been increasingly studied for their anticancer properties. This review presents the application of statins in cancer management by outlining the latest *in vitro* and *in vivo* studies. The results represent the foundation of the latest clinical trials in order to search for new treatment directions in cancer therapy.

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## INTRODUCTION

Statistics published in September 2018 by the World Health Organization revealed that cancer is responsible for one in six deaths worldwide. The most diagnosed and deadly types of cancer are lung cancer (LC), breast cancer (BC), colorectal cancer (CRC) and prostate cancer (PC). The most common risk factors responsible for cancer occurrence include smoking, obesity, unhealthy diet, alcohol consumption and viral infections<sup>[1]</sup>. Cancer, which is represented by a large number of conditions, is defined as an uncontrolled proliferation of cells that possess metastatic properties. These cells are characterized by changes in their activity, such as the suppression of apoptotic mechanisms, the disruption of cell adhesion and signaling, and changes that occur as a result of genetic mutations<sup>[2]</sup>.

Lately, high cholesterol levels have been associated with the development of some types of cancer, *i.e.*, CRC, PC and BC<sup>[3]</sup>. The literature describes two main paths through which cholesterol contributes to cancer onset. The first one involves the fundamental role of cholesterol in processes such as cell adhesion and signaling, necessary for normal cell functioning, while the second one refers to its function as a precursor in the synthesis of sex hormones and other isoprenoid intermediates, responsible for the development of particular types of cancer<sup>[4,5]</sup>. The latest treatment directions suggest that this field should be further explored due to the benefits that cholesterol-lowering drugs can bring in cancer treatment<sup>[4]</sup>.

Statins are the first cholesterol-lowering agents discovered. Due to their significant ability to reduce cholesterol blood levels, international guidelines acknowledge statins as a first-line treatment for hypercholesterolemia<sup>[6]</sup>. By inhibiting the synthesis of cholesterol and its metabolites<sup>[7,8]</sup>, statins have shown antiproliferative effects in various types of cancer<sup>[9]</sup>. A number of observational studies reported a risk reduction in the onset of cancer, or improvements in the outcomes of cancer, in statin users. The variable efficacy of different statins is related to their distinct physiochemical properties and the length of treatment<sup>[9]</sup>. Many *in vitro* and *in vivo* studies performed on different types of cancers underlined the molecular mechanisms through which statins inhibit cancer cell proliferation and metastasis<sup>[10]</sup>. These mechanisms were considered the basis for introducing statins in cancer treatment and prevention<sup>[8,11]</sup>. The antiproliferative effects of statins are a result of both inhibition of the mevalonate pathway and their pleiotropic effects, *i.e.*, antioxidant, anti-inflammatory and immune modulatory properties, with a major impact on patient survival and cancer recurrence<sup>[10,12]</sup>.

The purpose of this review was to present the latest studies regarding the antiproliferative effects of statins. The paper is divided into two parts. The first section is dedicated to reviewing the latest published preclinical studies, highlighting the main mechanisms through which statins exert their anticancer properties. In the second part, several observational studies and clinical trials on statins, as single therapy or in combination with anticancer therapies, are summarized as future lines of research in cancer prevention/treatment.

## MECHANISM OF ACTION OF STATINS

Cholesterol along with isoprenoid intermediates are synthesized through the mevalonate pathway. In this process, 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) is converted into mevalonate *via* HMG-CoA reductase. Statins, due to their structural similarity to HMG-CoA, are competitive inhibitors of HMG-CoA reductase, and thereby have the ability to suppress cholesterol synthesis<sup>[13-15]</sup>. The affinity of statins for HMG-CoA reductase is in the nanomolar range, compared to the natural substrate whose concentration needs to be in the micromolar range<sup>[15]</sup>. Statins mainly act in the liver, where they induce an overexpression of low density lipoprotein (LDL) receptors at the surface of hepatocytes, thereby increasing the uptake of circulating LDL<sup>[15,16]</sup>. Through this mechanism, statins reduce lipoprotein blood levels,

and consequently decrease the risk of developing cardiovascular diseases and their related complications<sup>[14]</sup>.

The potency of these drugs is highly influenced by their physicochemical properties. Lipophilic statins, *i.e.*, simvastatin, mevastatin, lovastatin, and pitavastatin, can easily cross cell membranes by diffusion, while hydrophilic statins, *i.e.*, pravastatin, need special membrane transporters<sup>[12,15,17,18]</sup>. Another difference arises due to their molecular structure. Synthetic statins, *i.e.*, rosuvastatin, pitavastatin, atorvastatin and lovastatin, possess a fluorophenyl group which confers them the ability to form an additional linkage to HMG-CoA reductase; therefore, exhibiting a more potent inhibition. On the other hand, simvastatin, pravastatin, mevastatin and lovastatin are obtained through fungal fermentation, and contain a decalin ring<sup>[13,15,18]</sup>. In addition, simvastatin and lovastatin are used as inactive prodrugs which makes them 100-fold more lipophilic than pravastatin. After oral administration, these prodrugs are metabolized by CYP enzymes to a hydroxy-acid active form<sup>[19]</sup>.

## PRECLINICAL STUDIES EVALUATING THE ANTICANCER EFFECTS OF STATINS

Since the first reports in the late 1990s on the ability of statins to influence cancer progression, their anticancer properties have been extensively documented in a wide range of cancer cell lines and tumor-bearing animal models. Several preclinical studies support the anticancer effects of statins against various types of tumors, including liquid tumors such as myeloma and leukemia, and solid tumors<sup>[20]</sup>. The possible underlying mechanisms that account for the anticancer effects have been reported in numerous *in vitro* studies. It has been shown that their anticancer properties result from the suppression of tumor growth, induction of apoptosis and autophagy, inhibition of cell migration and invasion, and inhibition of angiogenesis<sup>[21-23]</sup>.

This chapter outlines the current state of knowledge concerning the anticancer effects of statins from *in vitro* and *in vivo* preclinical studies. However, due to the vast data available in the literature regarding this subject, we will focus on presenting the most recent reports.

### *In vitro* studies

Some of the most recent results from *in vitro* studies on statin anticancer activity are presented in **Table 1**. By examining the results reported in the literature, several conclusions can be drawn, which are in agreement with findings previously reported by Osmak *et al.*<sup>[11]</sup>, Ahmadi *et al.*<sup>[24]</sup>, and others.

Firstly, it appears that the antitumor potential depends on the physicochemical properties of the statins, more precisely their lipophilicity. The chemical structure of the molecule dictates the solubility of the statin, which in turn will affect the pharmacokinetic profile<sup>[19,23,25]</sup>. The lipophilicity promotes access to different tissues, including cancer cells. Statins are taken up into cells by the organic anion-transporting polypeptide OATP1B1 mainly expressed by hepatocytes and for lipophilic statins also by passive diffusion through the membrane. As a result, hydrophilic statins show an increased affinity for hepatic tissue, but not for other tissues. However, lipophilic statins achieve higher levels in extrahepatic tissues where they interfere with the synthesis of cholesterol<sup>[19,24,26]</sup>. Several *in vitro* studies on various cancer cell lines have reported lower anticancer efficacy for hydrophilic statins as opposed to lipophilic statins. Beckwitt *et al.*<sup>[27]</sup> assessed the anticancer activity of four statins, namely atorvastatin, simvastatin, rosuvastatin, and pravastatin, on four types of cancer cell lines derived from primary tumors: Breast (MCF-7 and MDA-MB-231), prostate (DU-145), brain (SF-295), and melanoma. Atorvastatin displayed the highest antitumor effect, while pravastatin had the lowest efficacy at suppressing tumor growth in all the above-mentioned cell lines. Furthermore, rosuvastatin was less potent than atorvastatin, even though the former shows similar affinity for the enzyme HMG-CoA reductase. Simvastatin, on the other hand showed similar efficacy to atorvastatin<sup>[27]</sup>. Consistent with these findings, another study demonstrated that lipophilic simvastatin significantly inhibited the proliferation of esophageal adenocarcinoma OE-19 cells and esophageal squamous cell carcinoma Eca-109 cells, at concentrations of 30  $\mu\text{mol/L}$ , accompanied by the down-regulation of COX-2 and PGE2 in both cancer cell lines, in a dose-dependent manner. However, hydrophilic pravastatin had no obvious suppressive effect on tumor growth in the two investigated esophageal cancer cell lines<sup>[28]</sup>. In pancreatic cancer cell lines (PA-TU-8902, MiaPaCa-2, BxPC-3), except for pravastatin, all investigated lipophilic statins, at a concentration of 12  $\mu\text{mol/L}$ ,

**Table 1** *In vitro* studies on the anticancer potential of statins

Cancer type	Cancer cell line	Statin	Observations	Changes in intracellular signaling pathways	Ref.
Hepatoma	HepG2, Hep3B	Simvastatin	Inhibition of cell growth in a dose- and time-dependent manner; G0/G1 cell cycle arrest; Apoptosis	AMPK activation and STAT3/Skp2 axis suppression, inducing p21 and p27 accumulation	[21]
Ovarian cancer	Hey, SKOV3	Atorvastatin	Dose-dependent antiproliferative effect (1-250 $\mu\text{mol/L}$ ); Decrease in size and density of the cancer cells, and colony forming ability (at 150 $\mu\text{mol/L}$ ); G1-phase cell cycle arrest and S-phase decrease (at 150 $\mu\text{mol/L}$ ); Induction of apoptosis; Increased ROS levels in a dose-dependent manner; Induction of autophagy; Inhibition of cell adhesion and invasion	Inhibition of Akt/mTOR and activation of MAPK pathway; Decreased Mcl-1 expression, variable effect on Bcl-2 expression, increased cleaved PARP protein expression; Increased expression of cellular stress protein (PERK and Bip) (at 150 $\mu\text{mol/L}$ ); Reduced expression of VEGF protein and MMP-9	[22]
Breast cancer	SUM149, SUM159, MDA-MB-231	Simvastatin	Inhibition of proliferation, decrease in S-phase and increase in G1/S-phase arrest; Suppression of cell migration; Decrease in tumor sphere formation	Down-regulation of phosphorylated FOXO3a in SUM149 and SUM159 cells; Variable effect on total FOXO3a expression	[43]
Endometrial cancer	ECC-1, Ishikawa, primary cultures of endometrial cancer cells	Simvastatin	Dose-dependent antiproliferative effect in both cancer cell lines (0.01-50 $\mu\text{mol/L}$ ), and in 5/8 primary cultures; G0/G1-phase cell cycle arrest, decreased S-phase in ECC-1 cells; Decreased HMG-CoA reductase activity; Induction of apoptosis; Increased DNA damage, cellular oxidative stress; Reduced cell adhesion and invasion	Inhibition of MAPK pathway, differential effects on the Akt/mTOR pathway; Increased cleaved caspase-3, decreased Bcl-2 expression, unmodified Mcl-1	[20]
Osteosarcoma	MNNG/HOS	Simvastatin	Dose- and time-dependent antiproliferative effect (0.5-64 $\mu\text{mol/L}$ ); Dose-dependent morphological changes in treated cells: Cell shrinkage, loss of intercellular contact, reduced cell adherence, floating shapes; Dose-dependent suppression of cell migration, G0/G1-phase cell cycle arrest (16 $\mu\text{mol/L}$ ), and apoptosis	Dose-dependent down-regulation of MMP-2 and MMP-9; Down-regulation of cyclin D1, CDK2 and CDK4, up-regulation of CDKIs, p21 Cip1 and p27 Kip1; Decrease in PI3K and phospho-Akt expression, while total AKT remained unmodified, up-regulation of Bax and cleaved PARP expression, decreased Bcl-2 expression	[44]
Lung adenocarcinoma	A549, H1299, PC9, HCC827, H1975, H1435, PE8sc, CL1-0, Bm7, and immortalized normal lung epithelial cells (HBEC3KT)	Simvastatin	Higher cytotoxicity against LC cells with p53 mutation; Dose-dependent apoptosis; Reduced lipid rafts in mutant p53-bearing LC cells; Reduction in the migration distance; Promotes the nuclear transport of mutant p53 in Bm7 and H1435 cells	Increased levels of cleaved PARP and cleaved caspase-3; No difference in the level of LC3-II; Decreased level of p53, and increased level of high molecular weight HSP-40	[45]

MAPK: Mitogen-activated protein kinase; ROS: Reactive oxygen species; HMG-CoA reductase: 3-hydroxy-3-methylglutaryl-coenzyme A reductase; AMPK: AMP-activated protein kinase; STAT3: Signal transducer and activator of transcription 3; skp2: S-phase kinase associated protein 2; Akt: Protein kinase B; mTOR: Mammalian target of rapamycin; PARP: Poly (ADP-ribose) polymerase; VEGF: Vascular endothelial growth factor; MMP: Matrix metalloproteinase; CDK: Cyclin-dependent kinase; CDKI: Cyclin-dependent kinase inhibitor; PI3K: Phosphoinositide 3-kinase; LC3: Microtubule-associated protein 1A/1B-light chain 3.

displayed significant antiproliferative activity. Cerivastatin and simvastatin proved to be the most effective in suppressing tumor growth, followed by fluvastatin and lovastatin<sup>[29]</sup>. Jiang *et al.*<sup>[25]</sup> also proved the superior anticancer effect of lipophilic statins on BC (MDA-MB-231, MDA-MB-432, MDA-MB-435) and brain cancer (A172, LN443, U87, U118, U251), compared to hydrophilic rosuvastatin and pravastatin. Furthermore, the research group proved that the *in vitro* IC<sub>50</sub> of cerivastatin and pitavastatin can be achieved at therapeutic doses of 0.2-0.4 mg/d for cerivastatin, and 1-4 mg/d for pitavastatin, respectively. The clinical relevance of these observations is that for these two statins, the doses needed to inhibit tumor growth are in the same range as those used to control cholesterol levels<sup>[25]</sup>.

Secondly, statins exhibit anticancer effects with varying sensitivity depending on the type of tumor, as not all types of cancer cell lines are sensitive to statins. In one

study, atorvastatin was tested against seven different types of solid tumors, including ovarian (IGROV1, OVCAR3), breast (HS-578T, T47D), prostate (PC-3, DU-145), colon (HCT-116, KM-12), lung (HOP-92, NCI-H322M), brain (SF-295, SF-539) cancers, and melanoma (SK-MEL-5, MDA-MB-435). Atorvastatin affected the proliferation of these tumor cells differentially: The growth of some cell lines was fully or partially suppressed, while other cells were insensitive to atorvastatin treatment (at a concentration of 10  $\mu\text{mol/L}$ )<sup>[30]</sup>. These results suggest that the pharmacological effect is influenced by the genetic background of the cancer cells<sup>[25]</sup>. Using gene expression data from the above-mentioned fourteen cancer cell lines, and the results obtained from the sensitivity assay, Raghu *et al.*<sup>[31]</sup> were able to produce and validate a genetic signature which identifies statin-sensitive cells. Moreover, they demonstrated that statin-resistance is linked to increased E-cadherin (E-cad) expression on cancer cells. E-cad expressing cancer cells, namely epithelial and mixed epithelial-mesenchymal cancer cells (characteristic of primary and metastatic tumors) are inhibited at much higher statin concentrations than mesenchymal cancer cells (characteristic of circulating metastatic tumor cells). In this sense, Ishikawa *et al.*<sup>[32]</sup> screened atorvastatin against four cancer cell lines (two PC, and two LC cell lines) with different expressions of vimentin and E-cad. The sensitivity of the cells to atorvastatin decreased from sensitive mesenchymal PC-3 and HOP-92 cells to less sensitive epithelial NCI-H322M cells, and lastly resistant mixed epithelial-mesenchymal Du-145 cells. This suggests that statins preferentially inhibit the growth of mesenchymal-like cancer cells which are responsible for cancer dissemination and metastasis<sup>[32]</sup>. In a recent study, Hong *et al.*<sup>[33]</sup> tested the sensitivity of eight gastric cancer (GC) cell lines to simvastatin, in order to identify potential biomarkers of statin sensitivity. Half of the cell lines (SNU5, SNU719, SNU16, AGS) responded to simvastatin treatment, while the remaining (MKN45, SNU620, SNU668, NCL-N87) proved insensitive. Furthermore, the expression of thiamine pyrophosphokinase-1 (TPK1) was significantly increased in the simvastatin-sensitive cell cultures, suggesting that the TPK1 gene could be a valuable predictive biomarker of statin anticancer therapy efficacy<sup>[33]</sup>.

Lastly, given their anticancer potential, a large number of studies have proposed the association of statins to standard chemotherapy agents. In most cases, an additive or synergistic effect was observed for the combination therapy. Henslee *et al.*<sup>[34]</sup> investigated the antitumor effect of various statins (fluvastatin, atorvastatin, simvastatin, lovastatin, mevastatin, and pravastatin) in combination with doxorubicin, paclitaxel, or topotecan as a new treatment strategy in natural killer cell leukemia. Fluvastatin and atorvastatin inhibited cell growth in a dose-dependent manner, but in combination with different chemotherapy agents, a significantly greater cytotoxic effect was observed compared to the single drug treatment. In another study, simvastatin and mevastatin exhibited strong synergistic effects with doxorubicin against CRC. The cytotoxicity of doxorubicin was greatly enhanced in doxorubicin-resistant LoVo cancer cells, but there was little change in sensitive LoVo cells. Both statins promoted the accumulation of doxorubicin in LoVo cells, possibly through the induction of MDR1 gene expression which codes for P-glycoprotein<sup>[35]</sup>. Furthermore, simvastatin and atorvastatin, at a concentration of 12.5  $\mu\text{mol/L}$ , which did not induce significant cytotoxicity, enhanced the effect of bortezomib in multiple myeloma U266 cells. In addition, simvastatin displayed superior activity to atorvastatin<sup>[36]</sup>.

Several studies were conducted to evaluate the antitumor potential of lovastatin in combination with chemotherapy drugs such as cisplatin, 5-fluorouracil, daunorubicin, enzastaurin, and temozolomide, in various tumor cell lines. Lovastatin enhanced the cytotoxic effect of these drugs<sup>[24,37]</sup>. Enhanced antitumor effects were reported for simvastatin in combination with cisplatin, doxorubicin, gefitinib, vemurafenib/selumetinib in nasopharyngeal carcinoma, bladder cancer, non-small cell LC, and melanoma, respectively<sup>[24,38,39]</sup>.

The combined treatment of a statin (atorvastatin, pitavastatin) and a tyrosine kinase inhibitor (TKI) such as gefitinib, erlotinib, or sorafenib, displayed increased antitumor activity in TKI-resistant hepatocellular carcinoma (HCC), and non-small cell LC<sup>[40-44]</sup>.

### ***In vivo preclinical studies***

In addition to their *in vitro* efficacy, statins have been shown to exhibit anticancer effects *in vivo*, in various models of cancer in animals. The anticancer effects of statins have been mostly demonstrated in xenograft animal models, after the inoculation of cancer cells in rodents. Jiang *et al.*<sup>[25]</sup> investigated the anticancer effect of pitavastatin and fluvastatin on glioblastoma in a xenograft mouse model. The results showed that pitavastatin was superior to fluvastatin in inhibiting tumor growth, on account of the different physicochemical and biopharmaceutical properties of the two molecules (lipophilicity, rate and efficacy of absorption *etc.*). At the same time, this study

indicated that intraperitoneal injection improved the efficacy of pitavastatin, compared to oral administration, although the oral dose was higher<sup>[25]</sup>.

Ali *et al*<sup>[40]</sup> reported the efficacy of atorvastatin as an antitumor agent against non-small cell LC in NSG mice. Daily atorvastatin administration suppressed tumor growth in mice carrying TKI-resistant PC-9GR, H1975 and H1703 xenografts, by 59%, 48% and 57%, respectively, compared to their vehicle counterparts. The reduced tumor sizes in the atorvastatin-treated group corresponded to loss of Cav1 and GLUT3, induced pro-apoptotic Bax, and lowered tumor cholesterol content. Furthermore, glucose levels were significantly reduced following atorvastatin treatment, compared to vehicle treatment. The antitumor activity of atorvastatin *in vivo* was also verified in a transgenic mouse model expressing the clinically relevant EGFR T790M/L858R mutation, in which at treatment termination, atorvastatin-exposed animals showed an approximately 33% decrease in tumor mass compared to vehicle-treated transgenic mice. These data support the promise that statins are candidate drugs for TKI-resistant non-small cell LC treatment<sup>[40]</sup>.

Of all the HMG-CoA reductase inhibitors, simvastatin is one of the most investigated and documented statins. The anticancer effect of simvastatin was demonstrated in xenograft mouse models of osteosarcoma, HCC, and CRC, following intraperitoneal or oral administration<sup>[21,45,46]</sup>. According to the immunohistochemical analysis of tumor tissues, simvastatin exhibited its tumor growth suppressing effects by increasing p21 and p27 expression, and AMPK activation, decreasing Skp2 expression and STAT3 phosphorylation<sup>[21]</sup>, or upregulating the expression of BMP2<sup>[46]</sup>.

Many animal studies suggest that statins suppress BC progression. Ahern *et al*<sup>[47]</sup> reported that simvastatin, administered orally, impairs the growth of human breast tumor xenografts in mice by increasing PTEN expression and inducing apoptosis. In another study, a significant antitumor effect was observed in mice bearing ErbB2 transformed MCNeuA mammary cancer, after the daily oral intake of simvastatin or fluvastatin. Even though both statins significantly inhibited tumor growth *in vivo*, fluvastatin was slightly more effective than simvastatin. Immunohistochemical studies on these MCNeuA tumors demonstrated that the *in vivo* antitumor effect was due to a statin-induced decline in tumor cell proliferation (decreased Ki67 staining) and survival (increased cleaved caspase-3 staining)<sup>[48]</sup>.

The effects of statins and their underlying cellular mechanisms in the chemoprevention of CRC in suitable animal models of both sporadic and colitis-associated CRC have been reported by Pikoulis *et al*<sup>[49]</sup>.

In addition to tumor xenograft animal models, the anticancer efficacy of statins has also been reported in chemical-induced tumors in animals. Li *et al*<sup>[47]</sup> reported the ability of statins to reverse adriamycin-induced cancer stem cell properties and metastasis in osteosarcoma by down-regulating KLF4 using a BALB/c (nu/nu) mouse model. Animals treated only with adriamycin showed a large increase in tumor incidence, supporting the idea that adriamycin can promote tumorigenesis of osteosarcoma cells. Tumor incidence in the adriamycin plus simvastatin group was much lower than that of the adriamycin group. Immunohistochemical analysis demonstrated that simvastatin blocks the adriamycin-mediated activation of KLF4 and CD133, and its tumor-initiating ability<sup>[50]</sup>.

Statins have also been shown to reduce metastasis *in vivo*, in various types of cancer. Liu *et al*<sup>[51]</sup> demonstrated, in a nude mouse model, that simvastatin significantly prevents the formation of osteolytic lesions caused by the metastasis of human A549 LC cells to the bone. This effect of simvastatin may be the result of its action on colonized LC cells in the bone, inhibiting the production and secretion of osteoclastogenic factors. It was shown that simvastatin attenuated the expression of CD44, a cell surface antigen enriched in epithelial tumor-initiating and metastatic cancer cells, which regulates the migration and invasion of LC cells. Simvastatin could increase the levels of p53 in A549 cells to repress the expression of CD44, and down-regulate MMP2 and MMP9<sup>[51]</sup>.

Furthermore, studies have demonstrated that statins increase the efficacy of chemotherapy *in vivo*. Atorvastatin restored sensitivity to different anticancer agents (*i.e.*, temozolomide, sorafenib) in mouse models of glioblastoma and HCC<sup>[41,52]</sup>. The overexpression of ABC transporters is generally associated with resistance to chemotherapy, which is prominently mediated by transporters like ABCB1, ABCC1, and ABCG2. Atil *et al*<sup>[53]</sup> conducted experiments on two xenograft mouse models to demonstrate the antitumor activity of simvastatin by ABCB1 down-regulation and apoptosis induction. CD-1 Nu/Nu mice inoculated with rhabdomyosarcoma or neuroblastoma cells received clinically relevant simvastatin concentrations and showed marked induction of apoptosis in both tumor tissues, indicated by PARP and caspase-3 cleavage. ABCB1 down-regulation was found in the liver and tumor tissues

but did not reach significance in neuroblastoma. The extend of apoptosis was comparable to that induced by cyclophosphamide, and was further amplified by the combination of the two drugs<sup>[53]</sup>.

## THE CLINICAL EXPERIENCE WITH STATINS IN ONCOLOGY

Statins are widely used for the control of hypercholesterolemia; thus, extensive data are available regarding cancer incidence and mortality in patients using statins. Despite this, the reported results are quite controversial. Initially, an increase in cancer incidence and cancer-related mortality was reported, but in recent years an opposite or lack of effect was observed in cancer patients using statins<sup>[54]</sup>. A possible explanation for these questionable results stems from the primary goal of the clinical trials, in which statins were considered for their effect on cardiovascular morbidities, and not on cancer incidence. These controversial results were first observed in animal studies, where a dose-response dependence on the onset/suppression of particular cancers was reported<sup>[6]</sup>. For more conclusive results regarding the impact of statin use on the incidence of cancer, the forthcoming clinical trials should include the identification of preexisting cancers and other confounding factors<sup>[55]</sup>.

Preclinical studies on statin anticancer efficacy highlighted the need to reach concentrations in the micromolar range in order to inhibit cell proliferation, concentrations that are unattainable in clinical practice without inducing side effects. Given this fact, statin use as single therapy for cancer treatment is questionable, but their association with standard chemotherapeutic agents for a synergistic or additive effect seems to be a feasible strategy for cancer therapy<sup>[6]</sup>. The statins currently available on the market are atorvastatin, rosuvastatin, pravastatin, pitavastatin, simvastatin and fluvastatin<sup>[54]</sup>. The anticancer potential of statins has been demonstrated mostly in PC and BC, but their effects on other solid malignancies, such as LC, CRC, and GC, are also noteworthy.

### PC

PC is the most common type of cancer and the leading cause of cancer-related death among men, in many countries<sup>[56]</sup>. Acute or chronic inflammation is the main cause not only of carcinogenesis but also the progression of PC. Thus, drugs and diets that suppress the inflammatory response or modulate the immune status have been reported to be beneficial for PC. Statins have great potential in preventing PC progression, as some studies have shown that statin use is associated with a reduction in PC risk<sup>[57]</sup>. On the other hand, the onset of PC is tightly associated with risk factors like obesity, hypertension, increased levels of testosterone, race, and family history<sup>[58]</sup>. Some of these risk factors are also linked to cardiovascular diseases and their related complications, as previously mentioned in this review. At present, the most efficient therapy for PC is androgen deprivation<sup>[58]</sup>. This therapy is based on the ability of PC cells to synthesize androgen hormones *de novo* due to the high levels of circulating cholesterol and on the *de novo* synthesis of cholesterol. Since cholesterol is a precursor in androgen synthesis, by inhibiting this pathway, statin therapy was considered a potential strategy to improve the outcomes in PC. In cancer, cholesterol is not only associated with the synthesis of sexual hormones, but is also responsible for cell growth, progression, proliferation and migration. Thus, statins can improve the outcomes of PC therapy by increasing the survival rate and decreasing the progression and recurrence of the tumor<sup>[59-62]</sup>. In addition, due to their anti-inflammatory properties, statins have the ability to inhibit the overexpression of androgen receptors, which in turn leads to suppression of cell growth<sup>[59,60]</sup>.

It was also observed that androgen deprivation combined with radiotherapy increases the survival rate<sup>[58]</sup>. *In vivo* and *in vitro* studies revealed a synergistic effect between statin therapy and radiotherapy, mainly by cell death. This combination therapy caused a 30% reduction in mortality among statin users diagnosed with PC<sup>[63]</sup>.

The results regarding the effect of statins on PC risk were obtained mainly as secondary data from clinical trials evaluating the use of statins in primary or secondary prevention of cardiovascular disease<sup>[64]</sup>. A retrospective study published in 2014 showed that postdiagnostic use of statins was associated with a decreased risk of PC mortality and all-cause mortality, especially in patients who used statins before diagnosis<sup>[62]</sup>. Prospective studies examining the link between statin use and the risk of PC suggested that statins may not reduce the risk of PC but may lower the risk of advanced or high-grade disease<sup>[65]</sup>. However, as prostate-specific antigen (PSA) is the primary method for PC screening, and statin use is associated with lower PSA levels,

this confounds the associations between statins and the risk of being diagnosed with PC. To clarify this, the association between baseline statin use and the risk of overall, high-grade (Gleason  $\geq 7$ ) or low-grade (Gleason  $\leq 6$ ) PC *vs* no cancer was examined in a post-hoc secondary analysis of REDUCE, a prospective multinational randomized controlled trial of dutasteride *vs* placebo among men with elevated PSA and a negative PC biopsy at baseline. The conclusion of the study was that statins were not associated with the risk of being diagnosed with PC or high-grade disease<sup>[66]</sup>. The data from the REDUCE study were also used to test the correlation between statin users and prostate volume (PV) change over time, determined from transrectal ultrasonography performed to guide prostate biopsy at baseline, and 2- and 4-years after randomization. Statins were found to modestly attenuate PV growth, with a magnitude in line with previously reported PSA-lowering effects for these drugs (approximately 4%).

Taking into account the conflicting evidence regarding the role of statins in PC chemoprevention, a recently published cohort study performed in the United States evaluated the association of statin use with PC in terms of Gleason score (reflecting the aggressiveness of PC), time and dose dependence, based on electronic medical records. The conclusion of the study was that statins might be associated with a reduced PC risk only when used for a relatively longer time, and the risk reduction was higher for patients with higher Gleason score. Additionally, lipophilic statins were more protective than hydrophilic statins<sup>[67]</sup>.

Statins, administered preoperatively, were also evaluated in clinical studies for their influence on disease recurrence, proliferation index or tumor biomarker status, in men undergoing radical prostatectomy<sup>[68-70]</sup>. The statins investigated in these trials were simvastatin and atorvastatin, but the results have still to be published.

## BC

BC is the most frequently encountered cancer among women, and the number of clinical trials assessing the putative clinical benefit of statins in BC is increasing. Recently, a direct association between cholesterol blood levels and the incidence of BC was observed. A high level of LDL increases BC cell proliferation and induces gene changes that are not favorable for the prognosis of BC<sup>[71]</sup>. A 72% risk reduction in the onset of BC was observed among statin users, especially in estrogen-negative BC cases. This result has been reported in long-term statin therapy<sup>[72]</sup>. Additionally, statins were shown to reduce BC patient mortality, but the benefit appears to be dependent on statin type and follow-up time. Thus, lipophilic statins showed a stronger protective effect in BC patients, reflected by a significantly increased recurrence-free survival and an improved overall survival. On the other hand, hydrophilic statins only slightly improved all-cause mortality. Furthermore, the protective effect was observed only in groups with less than 4 years of follow-up<sup>[73,74]</sup>. Also, it has been shown that statins did not increase the risk of BC<sup>[75]</sup>.

More recent clinical studies have included the evaluation of tumor biomarkers capable of predicting statin response, in their design and analysis plan. Thus, a clinical trial investigated the effects of short-term (two weeks) administration of atorvastatin, at the maximum recommended dose, on the levels of conventional BC pathological biomarkers, *i.e.*, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor (HER2), as well as the cell cycle regulators cyclin D1 and p27. While ER, PR and HER2 expression remained stable following treatment, a significant decrease in cyclin D1 expression and a significant increase in p27 expression were observed. The results of this study suggested that cell cycle regulatory effects contributed to the antiproliferative effects of statins in BC<sup>[76]</sup>. Another ongoing clinical trial is exploring the relationship between the short-term use of oral simvastatin and changes in the expression of Ki-67 (a candidate biomarker of breast tumor proliferation), in women with clinical stage 1 or 2 primary invasive BC, but the results of this trial have not yet been published<sup>[77]</sup>. The same biomarker was the focus of another clinical trial, in which the administration of atorvastatin (80 mg/d) for two weeks led to a decrease in cell proliferation rate<sup>[47]</sup>.

Another objective in recent clinical studies is to exploit the antitumor activity of statins in combination with preoperative standard chemotherapy, associated or not with zoledronate (zol). For this purpose, atorvastatin was evaluated in a clinical trial of patients with triple negative BC. The clinical trial is to finish in 2020, and the expected outcomes are the efficacy endpoint and the proportion of responsive patients after 6 months of treatment, at surgery<sup>[78]</sup>. In another pre-surgical study, fluvastatin and atorvastatin were administered in high doses to BC patients with baseline overexpression of HMG-CoA reductase. Inhibition of cell proliferation was observed. There were no differences between lipophilic and hydrophilic statins, which suggested

that all statins act by inhibiting the mevalonate pathway<sup>[79]</sup>.

Exposure to potentially cardiotoxic BC therapies, including anthracyclines, trastuzumab, and radiation therapy, coupled with host factors, place patients at an increased risk of developing cardiovascular diseases (CVD) compared to non-cancer controls. Overall survival outcomes are significantly worse in patients who develop CVD, and cardiovascular death may even exceed the risk of cancer death in the long-term. In this context, there is a current trend to establish cardioprotective strategies at the time of cancer therapy initiation, and statins are among the proposed drugs<sup>[80]</sup>. The Preventing Anthracycline Cardiovascular Toxicity with Statins trial explores a new clinical paradigm to manage BC: Primary prevention of anthracycline-based adjuvant therapy-related left ventricular (LV) dysfunction using pre-treatment with statins. Thus, 279 patients with early stage BC or lymphoma, with normal baseline left ventricular ejection fraction (LVEF), and treated with anthracyclines, will receive 40 mg atorvastatin or placebo at the start of chemotherapy, and will be continued for 24 mo. The primary endpoint is LVEF maintenance at 24 mo. This study will also quantify measures of cardiac and vascular remodeling, including strain, wall thickness, LV volumes, fibrosis, and pulse wave velocity<sup>[81]</sup>. Another ongoing study will evaluate the use of simvastatin for prophylactic cardioprotection<sup>[23]</sup>. Besides anthracyclines, trastuzumab is another effective drug used to treat HER2+ BC, but it is associated with a risk of cardiac dysfunction. A retrospective case-control study based on electronic chart review of consecutive women with HER2+ BC, treated with trastuzumab-based therapy was carried out to evaluate whether exposure to statins during cancer treatment would have a lower decline in LVEF and lower incidence of cardiotoxicity, compared to those who were not exposed to statins. The results showed that the concomitant use of statins was associated with a lower risk of cardiotoxicity<sup>[82]</sup>. In another clinical study, the topical administration of atorvastatin 1% gel twice daily during radiotherapy significantly reduce itching, breast edema and pain in patients under treatment<sup>[83]</sup>.

### CRC

Accumulating evidence suggests that statins may have a role in CRC prevention and treatment, but associations between individual statin characteristics, their doses and CRC have not yet been defined. Rho and Ras proteins are overexpressed in this type of cancer, and by inhibiting their synthesis through the mevalonate pathway, cancer proliferation and invasion are suppressed<sup>[84]</sup>.

In many studies, statin use was associated with a 30% to 50% risk reduction in developing CRC<sup>[84-86]</sup>. A study analyzing data from the National Health Insurance Service-Health Screening (NHIS-HEALS) cohort in Korea, conducted by NHIS from 2002 to 2015, showed that statins might have different preventive activity against CRC, depending on the anatomical site of the tumor, and patient sex. Thus, the risk of developing CRC was lower in statin users with hypercholesterolemia, especially proximal colon cancer in men and rectal cancer in both sexes<sup>[87]</sup>. A meta-analysis of existing comparative studies published between 1990 and 2016 investigated the association between statin use and the risk of colorectal adenoma. According to this publication, statin use was associated with a reduced risk of advanced adenoma, but did not significantly reduce the risk of any adenoma. It appears that statins may prevent CRC by acting at the later stages of progression, rather than at the early stages of adenoma initiation and development<sup>[88]</sup>. As a result of affecting the later stages of the adenoma-carcinoma sequence, statins reduce the aggressiveness and invasiveness of CRC. This hypothesis is supported by various studies which report that statin therapy is associated with improved CRC-specific survival<sup>[89]</sup>.

Simvastatin was clinically evaluated in addition to standard XELIRI/FOLFIRI chemotherapy regimens, to assess whether it confers a clinical benefit to patients with previously treated metastatic CRC. However, the proposed treatment did not improve progression-free survival nor did it increase the toxicity of the conventional chemotherapy regimen<sup>[90]</sup>.

### Gynecologic cancers

Endometrial and ovarian cancers are the most common types of gynecological malignancies<sup>[91,92]</sup>. In most cases, it was observed that the mevalonate pathway plays a major role in the development of these two types of cancer. Farnesyl pyrophosphate and geranylgeranyl pyrophosphate, which are inhibited by statins, are involved in the modification of several regulatory proteins, including the Ras and Rho protein family. Changes in Ras and Rho protein expression are responsible for 20% and 40% of cases of endometrial and ovarian cancer, respectively<sup>[93]</sup>. Conflicting results have been reported by different studies regarding these two types of cancer. One study

concluded that while statin use reduced the risk of developing endometrial cancer, there was no influence on ovarian cancer<sup>[93]</sup>. Other studies reported a 50% risk reduction of developing ovarian cancer in statin users<sup>[94]</sup>. A meta-analysis published in 2018 evaluated the association between postdiagnostic statin use and ovarian cancer mortality, and, based on the analysis of eight cohort studies of ovarian cancer patients, a significant protective effect on overall and cancer-specific survival was observed<sup>[95]</sup>.

### HCC

HCC is the most common liver cancer with a high mortality worldwide<sup>[96]</sup>. A meta-analysis concluded that statin therapy can reduce the incidence of HCC by almost 37% in a time- and dose-dependent manner. It is worth noting that this result was observed only among statin users and not when other cholesterol lowering agents were used, implying that HCC risk reduction is more likely attributed to the pleiotropic effects of statins rather than to their cholesterol lowering properties<sup>[97]</sup>. Bearing this in mind, two clinical trials investigated the influence of pravastatin therapy on patient survival after transarterial embolization (TAE) of HCC. Due to its high affinity for hepatic tissue, pravastatin prolonged the survival of patients with HCC<sup>[98,99]</sup>. In addition, pravastatin also demonstrated hepatoprotective and tumor progression suppressive effects when administered in conjunction with TAE<sup>[99]</sup>.

### GC

Similar to HCC, GC has a decreased long-term survival rate, and occurs primarily due to specific lifestyle features<sup>[100]</sup>. A phase II clinical trial evaluated the antitumor effect of a high dose of lovastatin in advanced GC. No clinically significant response was observed, even if prior preclinical studies suggested otherwise and the highest dose of lovastatin was administered<sup>[101]</sup>. Another two clinical trials investigated the impact of adding a statin, namely simvastatin or pravastatin, to chemotherapy, on tumor progression rate or survival rate. Simvastatin was chosen for its effectiveness in a wide variety of cancers, while pravastatin was selected for its hydrophilic profile, which makes it available in high concentrations in peripheral tissues such as gastric tissue. However, no improvements in the outcome were obtained in either of the two trials<sup>[102,103]</sup>. The lack of efficacy against GC can be ascribed to the use of a low dose of statin or to extensive hepatic metabolism<sup>[101,102,104]</sup>.

### Other types of cancer

As the number of studies investigating the potential clinical benefits of statins in various types of cancer is very high, the conclusions of several recent meta-analyses addressing the most explored applications in cancer treatment are summarized in Table 2<sup>[105-110]</sup>. Based on the synergism reported for combinations of statins and cytotoxic drugs in preclinical studies, several clinical trials investigated the effect of adding statins to anticancer treatment in various types of cancer. Other clinical studies explored the impact of statin use on patient survival. However, the results of these studies were, to some extent, contradictory. The published meta-analyses are useful for an integrated conclusion, but a consensus whether statins are useful in oncology has not yet been reached.

In 2018, Abdullah *et al.*<sup>[111]</sup> concluded that the lack of success encountered especially in prospective clinical studies may be due to a poor design of these studies. The authors pointed to the necessity of including in subsequent clinical trials, several crucial factors (*i.e.*, the administered dose, schedule, choice of statin, and diet), previously identified in preclinical trials as essential for statins to be effective, in order to improve the outcome of cancer patients<sup>[111]</sup>.

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## CONCLUSION

It has been proven that in addition to its major implication in the promotion of cardiovascular diseases, cholesterol also plays a significant role in the onset of cancer. Based on these findings, statins, potent inhibitors of HMG-CoA reductase, used as first-line medication in the treatment of hypercholesterolemia, were considered for cancer treatment. *In vitro* and *in vivo* studies performed on many types of cancer highlighted the beneficial effects of statins in cancer prevention/treatment. The observed effects were highly dependent on statin physicochemical properties, potency, dose and treatment length. In most cases, lipophilic statins were preferred as they could easily cross cell membranes, and are efficiently taken up by cancer cells. Taking into consideration the results from preclinical studies and the high number of statin

Table 2 A summary of recent meta-analyses evaluating the benefits of statins in various types of cancer

Cancer type	No. of clinical trials and subjects included	Objective	Results	Ref.
Active cancer	Ten studies, 1881 individuals with stage 3 or higher disease	To evaluate the randomized controlled trials of statins in addition to standard anticancer therapy	The addition of statins to standard anticancer therapy did not improve overall survival or progression-free survival	[105]
Solid cancer	Eight randomized controlled trials, 1760 patients	To evaluate the effect of statins added to systemic anticancer therapy in patients with solid cancer	The addition of statins to chemotherapy did not significantly increase the incidence of grade 3-5 adverse events, did not improve the overall response rate and failed to prolong the progression-free survival and overall survival compared with that of chemotherapy alone	[106]
Pancreatic cancer	Six retrospective cohort studies, 12057 patients were included	To explore the association between statin and metformin use and overall survival of pancreatic cancer patients	Statin use was associated with a significantly improved overall survival (but with a significant publication bias)	[107]
	Twenty-six studies, more than 3 million participants, 170000 pancreatic cancer patients	The relationship between statin use and the risk of pancreatic cancer	Statins have a protective effect on pancreatic cancer	[108]
Kidney cancer	Twelve studies, 18105 patients	To evaluate the association between statin use and kidney cancer survival outcomes	Statin use was not associated with significant recurrence-free survival or progression-free survival; statin use was associated with marked improvements in cancer-specific survival and overall survival	[109]
Lung cancer	Seventeen studies, 98445 patients	To analyze the impact of statins on mortality and survival of LC patients	Statins were potentially associated with a decreased risk of mortality and an improvement of overall survival in observational studies but not in randomized controlled trials; Statins potentially enhanced the effects of tyrosine kinase inhibitors and chemotherapy on the overall survival of patients with non-small cell LC	[110]

users, observational clinical studies were performed in order to establish a direct linkage between statin therapy and risk reduction in the onset/recurrence of cancer. Studies have shown that there is a direct correlation between statin use and a reduced risk of cancer onset, or improvement in cancer outcomes. Most studies focused on PC, BC and CRC, because cholesterol plays a major role in these cancers, and reported statistically significant results. The positive results obtained from animal and clinical studies encouraged scientists to search for new directions in cancer treatment. Currently, statins are evaluated in many ongoing clinical trials on cancer patients. According to the published results, statin therapy shows some benefits in several types of cancer, with an increased survival rate, but other studies reported no effect. Therefore, more studies are needed to clarify these controversial results.

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