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Original Paper

Statins and Thyroid Carcinoma: a Meta-Analysis

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Key Words
Statin • Thyroid carcinoma • Proliferation • Apoptosis • Meta-analysis

Abstract
Background/Aims: Experimental studies have reported the antineoplastic effects of statins in thyroid carcinoma; however, observational studies suggested that statins might increase the risk of thyroid carcinoma. Therefore, this study evaluated the antineoplastic effects of statins in both *in vitro* studies and animal models, as well as the epidemiological evidence. ***Methods:*** Databases—PubMed, Cochrane Library, SinoMed, CNKI, Wanfang, and clinical trial registries—were searched. A meta-analysis was performed with sufficiently homogeneous studies. Eighteen articles were involved. ***Results:*** In *in vitro* studies, statins showed a concentration-dependent inhibition of cell line growth (weighted mean difference –34.68, 95% confidence interval –36.53 to –32.83). A significant efficacy of statin-induced apoptosis was observed (weighted mean difference [95% confidence interval]: 24 h, 57.50 [55.98–59.03]; 48 h, 23.43 [22.19–24.66]; 72 h, 51.29 [47.52–55.07]). Early apoptosis was increased in a dose- and time-dependent manner. In *in vivo* antitumor studies, lovastatin inhibited tumor growth, as shown by a reduction in tumor volume. However, two clinical studies showed discordant results from the experimental studies. ***Conclusion:*** Experimental studies revealed the antineoplastic efficacy of statins but statins were associated with thyroid carcinoma in clinical studies. This discrepancy may be due to the different concentrations of statins used and the effects of hyperlipidemia interventions, and thus further study is required.

Introduction

Statins, which inhibit hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase, are widely used for cardiovascular disease management due to their lipid-lowering effects. In addition to their ability to lower cholesterol and prevent primary and secondary cardiovascular diseases [1-4], statins have other effects unrelated to lipid reduction, such

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as inhibition of the growth of malignant cells [5-7]. The most interesting finding is the contradiction of their antineoplastic effect in experimental studies [8-23] and their potential carcinogenicity in clinical studies [24-25]. Some studies reported that statins inhibit the proliferation of thyroid cancer cells [11-14, 18-19, 22] and induce apoptosis [8, 10, 13-14, 17, 21] and differentiation [9, 14, 19]. However, clinical studies on this topic have incongruous results regarding whether statins are a risk factor for thyroid cancer [24-25]. These discrepancies may be partly due to differences in statin type and dose, cell lines, and treatment times. Clear determination of whether statins are antineoplastic or tumorigenic is required to exclude the chance for both patient and physician misunderstanding in clinical practice.

Therefore, the relationship between statins and thyroid carcinoma should be further explored not only via epidemic evidence, but also mechanistic experiments both *in vitro* and *in vivo*. In this systematic review, we analyzed and investigated the current evidence regarding statins and thyroid carcinoma risk in both cell and animal experiments and in clinical studies.

Materials and Methods

Search process

We searched the PubMed, Cochrane Library, SinoMed, CNKI, and Wanfang databases for *in vitro* (cell line) studies, animal studies, and clinical studies of statins in thyroid carcinoma. Trials registered at clinical trial registries (*http://www.clinicaltrials.gov*) were also searched. The literature search for this review was restricted to published results. Databases were searched from the earliest date until December 1st, 2017, with the following search terms: "hydroxymethylglutaryl coenzyme A reductase inhibitor" or "hydroxymethylglutaryl-CoA reductase inhibitors" or "HMG-CoA reductase inhibitors" or "statins" or "lipid-lowering agent(s)" or "atorvastatin" or "fluvastatin" or "lovastatin" or "mevastatin" or "pravastatin" or "pitavastatin" or "rosuvastatin" or "simvastatin" or "cerivastatin") and ("thyroid cancer*" or "thyroid neoplasm*" or "thyroid tumor" or "thyroid carcinoma*" or "differentiated thyroid carcinoma" or "DTC" or "papillary thyroid carcinoma" or "thyroid carcinoma, papillary" or "PTC" or "thyroid cancer, follicular" or "FTC" or "thyroid carcinoma, anaplastic" or "ATC" or "thyroid cancer, medullary" or "MTC". Reference lists of all eligible articles and related review articles were also searched.

Eligible studies met the following criteria: (1) published in English or Chinese; (2) assessed the effect of statins on thyroid carcinoma; (3) examined cell lines derived from thyroid carcinoma (*in vitro* study), animals with xenograft tumors modeled by subcutaneous inoculation with thyroid cancer cell lines (*in vivo* animal studies), or clinical studies including both observational studies and experimental studies; and (4) evaluated at least one baseline and post-treatment outcome.

Study selection and data extraction

Two reviewers independently screened the studies on the basis of title and abstract. Disagreements were resolved by evaluation of the entire publication and by discussion between the two reviewers. If the disagreement could not be resolved, another experienced reviewer made the final decision. From the eligible studies, the following data were extracted: (1) characteristics of cell lines (*in vitro* study), tumor transplantation animal models (*in vivo* animal studies), and trial subjects (in clinical trials); (2) type of intervention (including statin type and dose and therapy duration); and (3) main results and testing methods.

Statistical analysis

The main outcome in *in vitro* studies was the survival and apoptosis of thyroid carcinoma cell lines with statin exposure (including cell counts and apoptotic rate). Other outcomes, including cell viability and invasion, cell cycle analysis, and expression levels of thyroglobulin were collected to analyze *in vitro* studies. The main outcomes were the change in tumor volume from baseline in the *in vivo* studies of animals and the incidence of thyroid carcinoma in patients treated with statins in clinical trials. A fixed-effect model was performed using the weighted mean difference (WMD), standardized mean difference, and 95% confidence

interval (95% CI) for continuous variables. For dichotomous variables, a fixed-effect model was conducted by computing the odds ratio (OR) and 95% CI. The I^2 was calculated as an index of heterogeneity between studies. If the I^2 was higher than 50%, sensitivity analysis was performed to assess whether the results were significantly influenced by lower quality studies.

Quality assessment and risk of bias

Study quality and risk of bias were assessed via the recommendations published in 1999 [26]. This rating system was used to assess the methodological quality of the included *in vivo* animal studies. Studies with 4 or fewer points were graded as having "poor methodological quality", whereas those with higher than 4 points were grouped as having "good methodological quality". Two reviewers independently scored these items. Sensitivity analysis was performed for low-quality studies. Analyses were performed using Review Manager 5.3 (Cochrane Collaboration, United Kingdom, http://www.cochrane.org).

Results

Search results and description of studies

Our search process yielded 250 potentially relevant studies. After abstract screening, 55 articles were selected for full-text review. Of these, 18 articles including 20 studies were eligible. Among the final 18 articles, there were 14 *in vitro* studies, 4 *in vivo* animal studies, and 2 clinical trials. The search process is shown in Fig. 1. The main characteristics of the 20 studies are shown in Table 1, Table 2, and Table 3. Three types of cell lines were used in the *in vitro* studies: three involved human papillary thyroid carcinoma (PTC) cell lines (including P6, TPC-1, ONCO-DG-1, and B-CPAP), one involved differentiated rat thyroid cell lines (including FRTL-5, FRTL-5-K-Ras, and FRTL-5-H-Ras), and 10 involved human anaplastic thyroid carcinoma (ATC) cell lines (including ARO, FRO, KAT-4, THJ-16T, 8505C, BHT-101, 8305C, SW1736, KAT4B, and HTh74). Three types of statins were investigated in the *in vitro* studies: lovastatin (12 studies), simvastatin (1 study), and rosuvastatin (1 study). Four studies investigated the *in vivo* antitumor effects of statins.

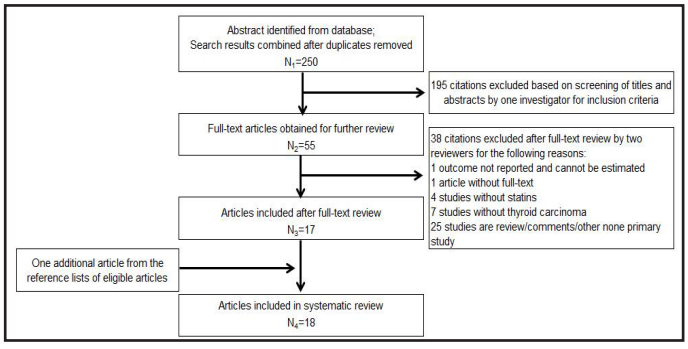

Fig. 1. Flow chart of the systematic search process.

Table 1. Characteristics of 14 included studies (in vitro)

First author, year of publication	Cell lines	Type of statins	Dose of statins (umol/L)	Intervention time of statins (hour)	Main results
Mario Vitale, 1999 [8]	Human PTC cell line: P6, TPC-1	Lovastatin	1,2,3,4,5,6,8,10	48	Apoptotic rate
Chin-Yuan Wang, 2003 [9]	Human ATC cell line: ARO	Lovastatin	10,25,50,75	6,12,24,48,72,96	Cell counts; Apoptotic rate
Wen-Bin Zhong, 2003 [10]	Human ATC cell line: ARO	Lovastatin	10,25,50,75	12,24,48	Apoptotic rate
Wen-Bin Zhong, 2005 [11]	Human ATC cell line: ARO	Lovastatin	20	18	Cell number; Invasion
Silvana Libertini, 2007 [12]	Human ATC cell line: FRO,KAT-4	Lovastatin	1,2.5,5	16	Cell survival
Chiara Laezza, 2008 [13]	Differentiated rat thyroid cell line: FRTL-5 (ATCC CRL 8305), FRTL-5-K-Ras, FRTL-5-H-Ras	Lovastatin	2,2.5,4,5,6,8,10	24	Cell number; Apoptotic rate; Cell cycle analysis
Eleonore Frohlich, 2009 [14]	Human PTC cell line: ONCO-DG-1 (primary tumor)	Lovastatin	200	48	Cell number; Apoptotic rate
Laura A. Marlow, 2010 [15]	Human ATC cell line: THJ-16T	Lovastatin	10	48	Apoptotic rate
Yoo Seung Chung, 2011 [16]	Human ATC cell lines: 8505C, BHT-101	Lovastatin	5,10,20,30,40	72	MTT-activity; Apoptotic rate
N Dilara Zeybek, 2011 [17]	Human PTC cell line: B-CPAP	Rosuvastatin	12.5,18.5,25,50, 100,200	48,72	Cell viability; Cell cycle analysis; Apoptotic rate
Wen-Bin Zhong, 2011 [18]	Human ATC cell line: ARO, 8305C, SW1736, KAT4B	Lovastatin	5,10,20	48	Cell number; Cell cycle analysis
Hao-Ai Shui, 2011 [19]	Human ATC cell line: ARO	Lovastatin	25,75	24	Cell number
Li-Han Chin, 2015 [20]	Human ATC cell lines: SW1736	Lovastatin	5,10,15,20	24	Cell viability; Migrated cells
Zhu Hui, 2015 [21]	Human ATC cell line: HTh74	Simvastatin	1,2,4,8	24,48,72	Cell proliferation rate; Cell clone formation; Apoptotic rate

Table 2. Characteristics of 4 included studies (in vivo)

First author, year of publication	Animal (treated/control), n	Type of thyroid cancer	Type of statins	Dose of statins (method of administration)	Main results (testing method)	Testing time	Score of methodological quality
Rodney L. Robison, 1994 [22]	Mice, 480/320 Rats, 450/300	Mice: Adenocarcinoma parafollicular Rats: Adenocarcinoma Follicular, Adenocarcinoma Parafollicular	Fluvastatin	Mice:50,150,350mg/kg/d; Rats: 6,9,18,24mg/kg/d. (not mentioned)	Incidence of thyroid cancer	83 weeks	5
Silvana Libertini, 2007 [12]	Mice, 20/20	FRO cells (4×10^6) were injected into mice	Lovastatin	10mg/kg/d*48d (per os)	Tumor volume	48 days	5
Chiara Laezza, 2008 [13]	Mice, 10/10	FRTL-5-K-Ras cells (1×10^6) were injected into mice.	Lovastatin	50mg/kg, three times a week for 4 weeks (intraperitoneally)	Tumor volume	4 weeks	5
Chih-Yuan Wang, 2010 [23]	Mice, 6/2	ARO cells (1.0×10^6) were implanted into mice.	Lovastatin	1,5,10 mg/kg/d (per os)	Tumor volume	30 days	5

Table 3. Baseline clinical parameters of patients (clinical studies)

First author, year of publication	Country of the study	Medication	Hazard ratio (95%CI) or Odds ratio(95%CI)	Following up
Gary D. Friedman, 2008 [24]	USA	Lovastatin, Simvastatin, Atorvastatin	Hazard ratio(95%CI): men (2 years): 1.19(0.70-2.05) men (5 years): 3.79(1.75-8.04) women (2 years): 0.87(0.57-1.32) women (5 years): 0.53(0.13-2.11)	2 years/more than 5 years
Shih-Han Hung, 2015 [25]	China	Unknown	Odds ratio(95%CI) men: 1.28(0.75-2.17) female: 1.43(1.07-1.90)	Unknown

Lovastatin and fluvastatin were used in these studies. Among these, three used a xenograft tumor animal model involving athymic mice inoculated with thyroid carcinoma cells. Lovastatin was intraperitoneally or orally administered with different concentrations and different intervention times. Either the number of patients treated with or without statins with thyroid carcinoma or the hazard ratio was collected for analysis. The methodological quality of the *in vivo* animal studies included in this meta-analysis was good according to the rating system used. Detailed information on the methodological quality score is shown in Table 2.

Outcomes

In vitro studies

Cell number. Of the 20 included studies, 8 reported the effect of statins on cell number and percentage. Among these, 4 studies showed the cell number results (% of the control) and presented the exact data (Fig. 2). The fixed-effect model was used to merge the WMD values, and the pooled effect size in favor of statins was –34.68 (95% CI –36.53 to –32.83), which means that statins significantly reduced cell number in thyroid carcinoma cell lines. Because different cell lines of thyroid carcinoma and different types and concentration of statins were used, there was considerable heterogeneity (heterozygosity test, chi-square = 545.58, $P < 0.00001$, $I^2 = 95\%$). Another four studies also showed the same results for cell number. According to the data from these studies, statins concentration-dependently inhibited the growth of thyroid carcinoma cell lines.

Cell viability. Two studies reported this parameter for lovastatin treatment of two cell lines (B-CPAP and SW1736). Because different concentrations of lovastatin were used in these two studies, the heterogeneity between these subgroups was significant (heterozygosity test, chi-square = 964.5, $P < 0.00001$, $I^2 = 99\%$). The pooled data were –39.50 (95% CI –42.07 to –36.92) (Fig. 3), which means that lovastatin can reduce the cell viability of thyroid carcinoma cell lines.

Apoptosis. Four studies including three types of statins (lovastatin, rosuvastatin, and simvastatin) were analyzed. Cells were treated with statins at different doses for different times and studies were subgrouped by the different durations of treatment (24 h, 48 h, and 72 h). Each subgroup showed a significant efficacy of statin-induced apoptosis (24 h, WMD 57.50 [95% CI 55.98–59.03]; 48 h, WMD 23.43 [95% CI 22.19–24.66]; 72 h, WMD 51.29 [95% CI 47.52–55.07]) and a concentration-dependent effect was observed (Fig. 4). Thus, statins can induce apoptosis in thyroid carcinoma cells.

Apoptosis quantification and cell cycle analysis. Seven studies reported the results of apoptotic analysis (including early apoptosis, late apoptosis, and necrosis) and cell cycle

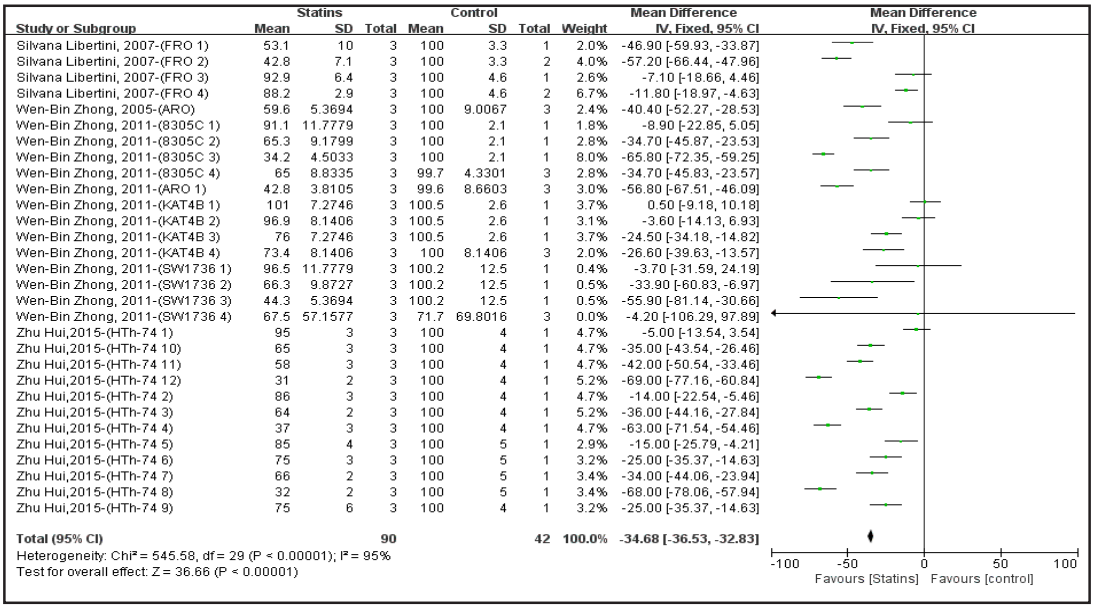

Fig. 2. Forest plot of the efficacy of statins on cell number (% of control) [11, 12, 18, 21].

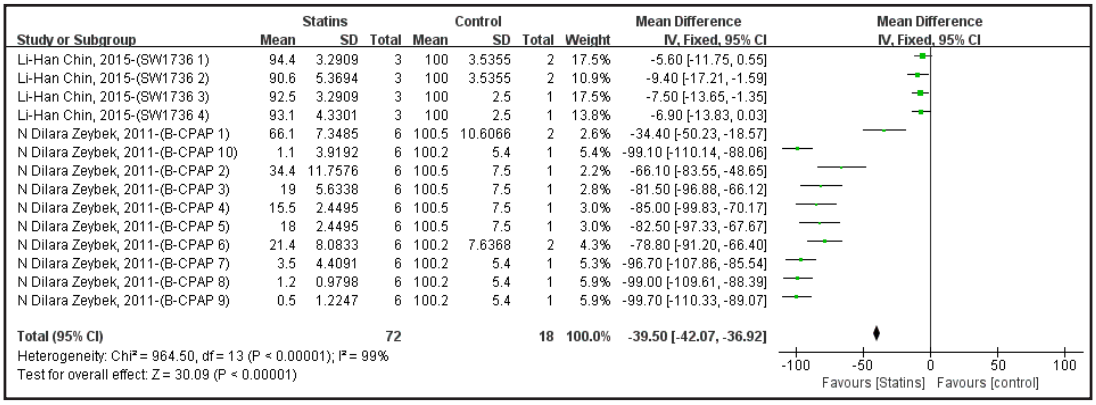

Fig. 3. Forest plot of the efficacy of statins on cell viability (% of control) [17, 20].

analysis of thyroid carcinoma cell lines treated with statins. Lovastatin (from 0 to 75 μmol/L) was used in all four studies that conducted apoptotic analysis. The remaining three reported cell cycle analysis using flow cytometry. The exact data showed that treatment of thyroid carcinoma cell lines with increasing concentrations and intervention times of lovastatin led to a dose- and time-dependent increase in early apoptosis (Table 4). Moreover, the difference was more significant in early-stage apoptosis than in late-stage apoptosis and necrosis. Furthermore, the same treatment induced a significant accumulation of cells at the G0/G1 phase of the cell cycle and a significant decrease in the number of cells in the S phase (Table 5).

In vivo antitumor effect of statins

Four studies investigated the *in vivo* antitumor effects of statins; three used a xenograft tumor animal model (lovastatin was used in all three studies). Tumor volumes in each group were compared and a substantial reduction in tumor growth was reported in lovastatin-treated mice compared with controls (data were not provided). This effect was also dose-dependent.

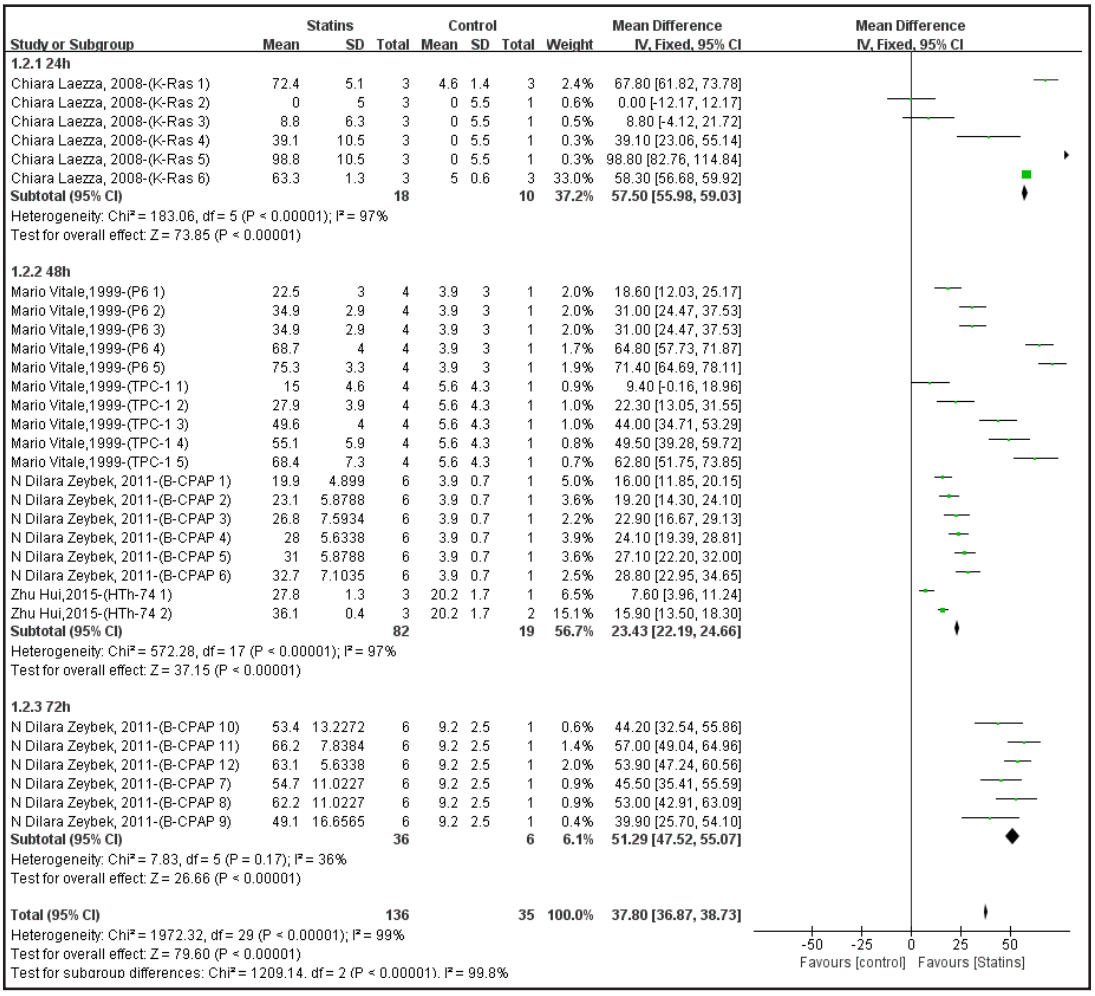

Fig. 4. Forest plot of the efficacy of statins on the percentage of apoptosis [8, 13, 17, 21].

Table 4. Quantification analysis of apoptosis in thyroid carcinoma cell lines treated with statins

First author, year of publication	Cell line	Statins (concentration, uM)	Time (hour)	Early apoptosis (%)	Late apoptosis (%)
Chin-Yuan Wang, 2003 [9]	ARO	lovastatin(50)	0	1.32	0.00
			6	45.36	10.01
			12	63.48	4.77
		lovastatin(50)	0	1.82	
			12	3.11	
			24	17.70	
			48	37.56	
Wen-Bin Zhong, 2003 [10]	ARO	lovastatin(0)		2.15	not mentioned
		lovastatin(10)		5.44	
		lovastatin(25)	48	14.03	
		lovastatin(50)		38.50	
		lovastatin(75)		48.57	
Laura A. Marlow, 2010 [15]	THJ-16T	lovastatin(10)	48	not mentioned	58.30
		lovastatin(0)		6.60	14.20
		lovastatin(5)		11.20	13.90
Yoo Seung Chung, 2011 [16]	8505C	lovastatin(10)	72	14.00	15.50
		lovastatin(20)		18.40	18.30
		lovastatin(30)		22.00	21.60
		lovastatin(40)		21.90	22.20

Clinical study of statins and thyroid carcinoma

Two clinical studies analyzed the relative risk of thyroid carcinoma associated with statins. Friedman et al. conducted a 9-year follow-up of 361, 859 statin recipients and found increased risk of thyroid cancer in male patients with more than 5 years of statin use (hazard ratio 3.79, 95% CI 1.75–8.04). In contrast, Hung et al. reported that statins were associated with thyroid cancer in female patients (OR 1.43, 95% CI 1.07–1.90) (Table 3).

Table 5. Cell cycle analysis in thyroid carcinoma cell lines treated with statins. Percents are means±S.E.M of independent experiments

First author, year of publication	Cell lines	Statins (concentration, umol/L)	Time (hour)	Apoptosis (%)	G0/G1(%)	S(%)	G2/M(%)
Chiara Laezza, 2008 [13]	FRTL5-H-Ras	lovastatin(0)	24	2.6	63	9	25.4
		lovastatin(10)		2.7	79.1	3.1	15.1
	FRTL5-K-Ras	lovastatin(0)		11.3	66.9	6.2	15.6
		lovastatin(10)		95.1	3.9	0.6	0.4
N Dilara Zeybek, 2011 [17]	B-CPAP	rosuvastatin(0)	48	4 ±0.33	57.9 ±1.5	26.6 ±0.4	15.5 ±1.0
		rosuvastatin(12.5)		28 ±3.17	71.0±1.5	17.7 ±1.2	11.3 ±0.9
		rosuvastatin(18.5)		34 ±14.3	75.0 ±1.3	12.9 ±0.9	12.1 ±1.5
		rosuvastatin(25)		91 ±2.62	77.0 ±1.3	15.0 ±0.8	8.9 ±1.7
		rosuvastatin(50)		89 ±6.91	78.2 ±1.4	13.2 ±0.6	8.6 ±1.3
		rosuvastatin(100)		81 ±11.1	79.1 ±1.7	0 ±0	20.9 ±1.5
		rosuvastatin(200)		98 ±1.52	83.7 ±1.6	0 ±0	16.3 ±1.7
		rosuvastatin(0)	72	4 ±0.33	59.1 ±1.5	20.9 ±0.5	20.0 ±1.0
		rosuvastatin(12.5)		6 ±2.00	74.4 ±1.0	2 ±0.5	23.6 ±1.0
		rosuvastatin(18.5)		13 ±1.00	75.0 ±1.2	15.0 ±0.8	10.0 ±1.0
		rosuvastatin(25)		60 ±0.50	77.7 ±1.2	10.0 ±0.3	6.1 ±1.1
		rosuvastatin(50)		92 ±1.00	79.8 ±1.3	10.0 ±0.8	12.0 ±1.0
		rosuvastatin(100)		45 ±13.37	79.1 ±1.5	8.9 ±0.6	12.0 ±1.0
		rosuvastatin(200)		66 ±1.00	85.0 ±1.8	3.9 ±0.4	11.1 ±1.2
Wen-Bin Zhong, 2011 [18]	ARO	lovastatin(0)	48	not mentioned	37.9±4.7	46.3±4.3	15.8±2.5
		lovastatin(20)			73.4±8.4	18.8±5.6	7.7±3.9
	8305C	lovastatin(0)			31.5±1.2	43.7±5.13	24.8±3.35
		lovastatin(10)			58.3±3.36	21.5±2.16	20.2±2.15
	SW1736	lovastatin(0)			42.7±2.11	32.4±4.24	24.9±4.33
		lovastatin(10)			63.5±3.18	24.6±1.37	11.9±2.07
	KAT4B	lovastatin(0)			30.5±1.04	53.6±4.63	15.9±2.5
		lovastatin(20)			68.5±2.44	17.8±2.86	13.7±1.77

Discussion

Cholesterol, an essential component of the cell membrane, is necessary for cell proliferation. An enzyme catalyzing the rate-limiting step of cholesterol biosynthesis is inhibited by statins [27]. In recent decades, several studies have found that statins have further effects beyond cholesterol. Besides lowering cholesterol and preventing primary and secondary cardiovascular diseases [1-4], they also have direct antioxidant, anti-inflammatory, and anticoagulant effects [7, 28]. Moreover, they may exert unexpected benefits on macrovascular diseases, osteoporosis, Alzheimer's disease, and other conditions. Another interesting finding is their potential antineoplastic effects [29-31].

In the present study, we summarized the efficacy of three types of statins (lovastatin, simvastatin, and rosuvastatin) in different thyroid cancer cell lines (including human anaplastic thyroid carcinoma, human papillary thyroid carcinoma, and rat differentiated thyroid carcinoma) and showed their value as an anticancer agent with antiproliferative and proapoptotic effects. In *in vitro* studies, statins inhibited the growth of thyroid carcinoma cells by reducing cell number and viability and increasing the rate of apoptosis. The antiproliferative effects could be due to increased G0/G1 phase arrest. Statin-induced apoptosis of thyroid cancer cells was concentration-dependent. Moreover, the difference was more significant in early-stage apoptosis than in late-stage apoptosis and necrosis. Results varied according to thyroid cancer cell line and treatment duration. Such different characteristics of cell lines and treatment time, as well as different dose of statins, might be the cause of the diverse results and heterogeneity. Meanwhile, the therapeutic effects of lovastatin on thyroid carcinoma in a nude mouse model were found by a reduction in tumor volume.

However, the antitumor efficacy findings remain controversial because clinical studies showed different results from experimental studies. Limited clinical studies showed that thyroid carcinoma was associated with statin use. This may be for a number of reasons. It has been reported that statins have dual effects on thyroid cancer cells, with different concentrations exerting different effects on cancer cells [9, 23]. A dose-dependent inhibition of cell survival was found when different concentrations of lovastatin were added to ARO cells (originating from an ATC patient). A lower concentration of lovastatin (10 μmol/L and 25 μmol/L) decreased proliferation but a higher concentration (50 μmol/L and 75 μmol/L) induced apoptosis and differentiation in the same cell lines [9]. Other *in vivo* evidence from a nude mouse caner model found that lovastatin inhibited tumor growth at a high dose (5

or 10 mg/kg/day) but significantly promoted it at a low dose (1 mg/kg/day) [23]. An oral dose of lovastatin of 4 mg/kg/day is a safe dose in clinical practice and can reach plasma concentrations of 0.1–3.9 μmol/L [32]. However, for experimental studies, the concentration of statins in cultured thyroid cancer cells varied from 8 to 200 μmol/L, which is much higher than that in human plasma with a routine dosage. This may explain the contradictory results between experimental studies and clinical studies. However, some clinical studies found that an oral dose of lovastatin of 25–30 mg/kg/day can be well-tolerated [32]. Unfortunately, data on statin concentration in human plasma and other potential risks for the ultra-high oral dose are still unknown. Because cholesterol is an essential component of the cell membrane in humans, the long-term ultra-routine overdose administration of statins might have more side effects. Moreover, research on the tolerance of long-term ultra-routine overdose of statins might be required.

In addition, most patients treated with statins have hyperlipidemia and the association of statins and thyroid cancer may be influenced by this concurrent condition. Hung et al [25]. found that the OR of thyroid cancer risk for prior hyperlipidemia among cases was 1.30 (95% CI 1.03–1.65) compared with patients without hyperlipidemia, which means that hyperlipidemia might be a risk factor for thyroid cancer. Recent studies have found that adipokines (e.g., interleukin-10) are a risk factor for differentiated thyroid carcinoma in women [33]. Rehem et al [34]. found that serum leptin levels were significantly higher in well-differentiated thyroid cancer patients than in control group patients, and a significant drop was detected after surgery. Moreover, the ratios of insulin-like growth factor-1 to adiponectin were positively associated with thyroid cancer tumor size [35]. Thus, hyperlipidemia, as well as adipocytokines, may play an important role in the relationship between statins and thyroid carcinoma.

In summary, the controversy surrounding the antitumor efficacy of statins might be due to the different concentrations of statins used and the potential relationship between hyperlipidemia and thyroid cancer. The association of statins and thyroid cancer is still unclear and further experimental and clinical studies are required.

In conclusion, our meta-analysis shows that statins can inhibit the growth of thyroid carcinoma cells *in vitro* by reducing cell number and viability and by increasing the level of apoptosis, particularly early apoptosis. In addition, statins play a role in reducing tumor volume in the xenograft tumor animal model. However, limited clinical studies showed an association between statins and thyroid carcinoma. The discrepancy may be due to the different concentrations of statins used and the potential risk of hyperlipidemia with thyroid cancer. These data may shed light on the underlying mechanisms of statin-based cancer therapy and could provide a rationale for the clinical use of statins as an auxiliary agent in patients with thyroid cancer. Meanwhile, the association between hyperlipidemia and thyroid carcinoma should be further studied.

Disclosure Statement

The authors declare no conflict of interests.

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